"525 Rec'd PCT/PTO" 0 5 JAN 2001

ATTORNEY'S DOCKET NUMBER FORM-PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV 10-2000) **GIN-6718CP5US** TRANSMITTAL LETTER TO THE UNITED STATES U.S. APPILICATION NO. (If known, see 37 CFR 1.5) DESIGNATED/ELECTED OFFICE (DO/EO/US) **CONCERNING A FILING UNDER 35 U.S.C.371** INTERNATIONAL APPLICATION INTERNATIONAL FILING DATE PRIORITY DATE CLAIMED 22 July 1999 (22.07.99) 24 July 1998 (24.07.98) PCT/JP99/03929 TITLE OF INVENTION HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE **PROTEINS** APPLICANT(S) FOR DO/EO/US Seishi KATO and Tomoko KIMURA Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information: 1. This is a **FIRST** submission of items concerning a filing under 35 U.S.C.371. 2. This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. This is an express request to bromptly begin national examination procedures (35 U.S.C. 371(f)). 4. The US has been elected by the expiration of 19 months from the priority date (PCT Article 31). 5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. \square is attached hereto (required only if not communicated by the International Bureau). b. **E** has been communicated by the International Bureau. c. \square is not required, as the application was filed in the United States Receiving Office (RO/US). 6. An English language translation of the International Application as filed (35 U.S.C 371(c)(2)). 17. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. \square are attached hereto (required only if not communicated by the International Bureau). b. \square have been communicated by the International Bureau. c. \square have not been made; however, the time limit for making such amendments has NOT expired. d. 🗷 have not been made and will not be made. 8. An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). Items 11. to 16. below concern document(s) or information included: 11. An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included 13. A FIRST preliminary amendment. ☐ A SECOND or SUBSEQUENT preliminary amendment. 14. A substitute specification. 15. A change of power of attorney and/or address letter. 16. Tother items or information: Transmittal Letter (2 sheets in duplicate); PCT Request and Fee Calculation Sheet (6 sheets); PCT Notification of Receipt of Record Copy (Form PCT/IB/301) (3 sheets); PCT Notification of Receipt of Search Copy (1 sheet); PCT Notification Concerning Submission of Priority Document (JP 10/208820 filed 24 July 1998) (PCT/IB/304) (1 sheet); PCT International Published Application (WO 00/05367) (without International Search Report) (351 sheets); Cover of PCT International Published Application (WO 00/05367) (with International Search Report attached) (12 sheets); PCT Notification of Transmittal of the International Search Report or the Declaration (14 sheets); PCT Notice Informing the Applicant of the Communication of the International Application to the Designated Offices (PCT/IB/308) (1 sheet); PCT Information Concerning Elected Offices Notified of their Election (PCT/IB/332) (1 sheet): PCT Notification of Receipt of Demand by Competent International Preliminary Examining Authority (1 sheet); PCT Written Opinion (NO RESPONSE NECESSARY) (4 sheets); Notification of Transmittal of the International Preliminary Examination Report (6 sheets); Check (#040892) (\$1130) based on large entity; Certificate of Express Mailing (1 sheet); and Return Postcard.

534 Neudruppru û 5 JAN 2001

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SEND ALL CORRESPONDENCE TO: Amy E. Mandragouras, Esq. LAHIVE & COCKFIELD, LLP 28 State Street SIGNATURE Peter C. Lauro NAME								
Boston, Massachusetts 02109 United States of America (617)227-7400 Date: 05 January 2001								

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WO 00/05367

PCT/JP99/03929

534 Rec'd PCT/PTO 0 5 JAN 2001

DESCRIPTION

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Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

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TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors for these DNAs as well as eucaryotic cells expressing these DNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against these proteins. The human cDNAs of the present invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by these cDNAs. Cells into which these genes are introduced to express secretory proteins and membrane proteins in large amounts can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular pharmaceuticals, and so on.

BACKGROUND ART

Cells secrete many proteins outside the cells. These secretory proteins play important roles for the proliferation control, the differentiation induction, the material transportation, the biological protection, etc. in the cells. Different from intracellular proteins, the secretory proteins exert their actions outside the cells, whereby they can be administered in the intracorporeal manner such as the injection or the drip, so that there are

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hidden potentialities as medicines. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents, etc. have been currently employed as medicines. In addition, secretory proteins other than those described above undergoing clinical trials to develop as pharmaceuticals. Because it has been conceived that the human cells still produce many unknown secretory proteins, availability of these secretory proteins as well as genes coding for them is expected to lead to development of novel pharmaceuticals utilizing these proteins.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. the material transportation and the information transmission through the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino acids, and so on, where the genes for many of them have been cloned already. It has been clarified that abnormalities of these membrane proteins are associated with a number of hithertocryptogenic diseases. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification from human cells, these secretory proteins and membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises introduction of a cDNA library into eucaryotic cells to express cDNAs and then screening of the cells secreting, or expressing on the surface of membrane,

PCT/JP99/03929

WO 00/05367

3

the objective active protein. However, this method is applicable only to cloning of a gene for a protein with a known function.

In general, secretory proteins and membrane proteins possess at least one hydrophobic domain inside the proteins, wherein, after synthesis thereof in the ribosome, domain works as a secretory signal or remains in the phospholipid membrane to be trapped in the membrane. the evidence of this cDNA for encoding a Accordingly, secretory protein and a membrane protein is provided by determination of the whole base sequence of a full-length cDNA followed by detection of highly hydrophobic domain(s) in the amino acid sequence of the protein encoded by this CDNA.

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OBJECTS OF THE INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors for these DNAs as well as transformed eucaryotic cells that are capable of expressing these DNAs. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

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BRIEF DESCRIPTION OF DRAWINGS

- Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01550.
- Fig. 2 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02593.
 - Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10195.

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- Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10423.
- Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10506.
- Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10507.
- Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10548.
- Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10566.
- Fig. 9 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10567.
- Fig. 10 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10568.
- Fig. 11 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01426.
 - Fig. 12 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02515.
 - Fig. 13 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02575.
 - Fig. 14 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10357.
 - Fig. 15 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10447.
- 25 Fig. 16 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10477.
 - Fig. 17 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10513.
 - Fig. 18 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10540.
 - Fig. 19 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10557.

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Fig. 20 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10563.

Fig. 21 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01467.

Fig. 22 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01956.

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Fig. 23 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02545.

Fig. 24 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02551.

Fig. 25 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02631.

Fig. 26 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02632.

Fig. 27 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10488.

Fig. 28 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10538.

Fig. 29 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10542.

Fig. 30 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10571.

Fig. 31 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01470.

Fig. 32 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02419.

Fig. 33 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02631.

Fig. 34 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02695.

Fig. 35 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10031.

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- Fig. 36 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10530.
- Fig. 37 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10541.
- Fig. 38 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10550.
- Fig. 39 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10590.
- Fig. 40 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10591.
- Fig. 41 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01462.
- Fig. 42 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02485.
- Fig. 43 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02798.
 - Fig. 44 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10041.
 - Fig. 45 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10246.
 - Fig. 46 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10392.
 - Fig. 47 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10489.
- Fig. 48 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10519.
 - Fig. 49 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10531.
- Fig. 50 illustrates the hydrophobicity/hydrophilicity 30 profile of the protein encoded by clone HP10574.

7

intensive studies, the present the result of inventors have been successful in cloning of cDNAs coding for proteins having hydrophobic domains from the human fulllength cDNA bank, thereby completing the present invention. In other words, the present invention provides human proteins hydrophobic having domains, namely proteins comprising any of the amino acid sequences represented by SEQ ID Nos. 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs comprising any of the base sequences represented by SEO ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140, as well as expression vectors that are capable of expressing any of these DNAs by in vitro translation or in eucaryotic cells and transformed eucaryotic cells that are capable of expressing these DNAs and of producing the abovementioned proteins.

DETAILED DESCRIPTION OF THE INVENTION

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The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the hydrophobic domains of the present invention, among which method for production with the recombinant technology is employed preferably. For instance, in vitro expression of the proteins can be achieved by preparation of an RNA by in vitro transcription from a vector having one of the cDNAs of the present invention, followed by in vitro translation using this RNA as a template. Also, introduction of the translated region into a suitable expression vector

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by the method known in the art leads to expression of a large amount of the encoded protein in prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

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In the case where one of the proteins of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro, when the translated region of this cDNA introduced into a vector having an RNA polymerase promoter, followed by addition of the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a extract, germ containing an RNA polymerase corresponding to the promoter. RNA polymerase promoters are exemplified by T7, T3, SP6, and the like. The vectors containing these RNA polymerase promoters are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II, and so on. Furthermore, the protein of the present invention can be expressed as the secreted form or the form incorporated into the microsome membrane, when a canine pancreas microsome or the like is added to the reaction system.

In the case where one of the protein of the present invention is produced by expressing the DNA in a microorganism such as Escherichia coli etc., a recombinant expression vector bearing the translated region of the cDNA of the present invention is constructed in an expression vector having an origin which can be replicated in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator etc. and, after transformation of the host cells with this expression vector, the resulting transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the

microorganism. In this case, a protein fragment containing any region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind the selected translated region. Alternatively, a fusion protein with another protein can be expressed. Only the portion of the protein encoded by this cDNA can be obtained by cleavage of this fusion protein with a suitable protease. The expression vector for Escherichia coli is exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system, and so on.

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In the case where one of the proteins of the present invention is produced by expressing the DNA in eucaryotic cells, the protein of the present invention can be produced as a secretory protein or as a membrane protein on the cellmembrane surface, when the translated region of this cDNA is introduced into an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) addition site, etc., followed by introduction into the eucaryotic expression vector is exemplified by pKA1, The pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian cultured cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, budding yeasts, fission yeasts, silkworm Xenopus oocytes, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eucaryotic cells by methods known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method, and so on.

After one of the proteins of the present invention is

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expressed in prokaryotic cells or eucaryotic cells, the objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

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The proteins of the present invention include peptide fragments (5 amino acid residues or more) containing any partial amino acid sequence in the amino acid sequences represented by SEQ ID Nos. 1. to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. These peptide fragments can be utilized as antigens for preparation of antibodies. Hereupon, among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins, after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal 8-187100 [JP Furthermore, A]. some proteins undergo the processing on the cell surface to be converted to the secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins to which sugar chains are attached. Accordingly, such proteins or peptides to which sugar chains are attached shall come within the

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scope of the present invention.

The DNAs of the present invention include all the DNAs coding for the above-mentioned proteins. These DNAs can be obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. These cDNAs are synthesized by using as templates poly(A)* RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available, human cDNA libraries can be utilized. Cloning of the cDNAs of the present invention from the cDNA libraries can be carried out by synthesis of an oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention, followed by screening using this oligonucleotide as the probe according to the colony or plaque hybridization by a method known in the art. In addition, the cDNA fragments of the present invention can be prepared by synthesis of oligonucleotides which hybridize with both termini of the objective cDNA fragment, followed by the usage of these oligonucleotides as the primers for the RT-PCR method using an mRNA isolated from human cells.

The cDNAs of the present invention are characterized by

WO 00/05367

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PCT/JP99/03929

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comprising either of the base sequences represented by SEQ ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or the base sequences represented by SEQ ID Nos. 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Table 1 summarizes the clone number (HP number), the cells from which the cDNA was obtained, the total base number of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1								
				Number				
SEQ ID No.	HP	Cells	Base	of amino				
	number		number	acid				
				residues				
1, 11, 21	HP01550	Stomach cancer	510	125				
2, 12, 22	HP02593	Saos-2	697	131				
3, 13, 23	HP10195	HT-1080	1619	242				
4, 14, 24	HP10423	U-2 OS	1066	264				
5, 15, 25	HP10506	Stomach cancer	618	112				
6, 16, 26	HP10507	Stomach cancer	1021	146				
7, 17, 27	HP10548	Stomach cancer	1432	344				
8, 18, 28	HP10566	Stomach cancer	601	97				
9, 19, 29	HP10567	Stomach cancer	585	124				
10, 20, 30	HP10568	Stomach cancer	1100	327				
31, 41, 51	HP01426	Stomach cancer	1065	313				
32, 42, 52	HP02515	Saos-2	937	229				
33, 43, 53	HP02575	Saos-2	1678	467				
34, 44, 54	HP10357	Stomach cancer	467	99				
35, 45, 55	HP10447	Liver	875	189				
36, 46, 56	HP10477	Liver	1256	363				
37, 47, 57	HP10513	Stomach cancer	884	249				
38, 48, 58	HP10540	Saos-2	589	98				
39, 49, 59	HP10557	Stomach cancer	673	172				
40, 50, 60	HP10563	Saos-2	1425	120				
61, 71, 81	HP01467	HT-1080	1436	307				
62, 72, 82	HP01956	Liver	997	183				
63, 73, 83	HP02545	Saos-2	1753	327				
64, 74, 84	HP02551	Saos-2	1117	223				
65, 75, 85	HP02631	Saos-2	1380	48				
66, 76, 86	HP02632	HT-1080	1503	371				
67, 77, 87	HP10488	Liver	733	90				
68, 78, 88	HP10538	Saos-2	3768	499				
69, 79, 89	HP10542	Stomach cancer	770	106				
70, 80, 90	HP10571	Stomach cancer	1229	152				

91, 101, 111	HP01470	Stomach cancer	1619	358
92, 102, 112	HP02419	Stomach cancer	2054	226
93, 103, 113	HP02631	Saos-2	1380	195
94, 104, 114	HP02695	Stomach cancer	1292	339
95, 105, 115	HP10031	Saos-2	2168	487
96, 106, 116	HP10530	Saos-2	1357	393
97, 107, 117	HP10541	Stomach cancer	711	196
98, 108, 118	HP10550	Stomach cancer	651	107
99, 109, 119	HP10590	HT-1080	1310	350
100, 110, 120	HP10591	HT-1080	1400	107
121, 131, 141	HP01462	HT-1080	2050	483
122, 132, 142	HP02485	Stomach cancer	2746	334
123, 133, 143	HP02798	HT-1080	1136	267
124, 134, 144	HP10041	Saos-2	619	106
125, 135, 145	HP10246	КВ	864	224
126, 136, 146	HP10392	U-2 OS	1527	258
127, 137, 147	HP10489	Stomach cancer	659	110
128, 138, 148	HP10519	Stomach cancer	710	91
129, 139, 149	HP10531	Saos-2	2182	344
130, 140, 150	HP10574	Stomach cancer	2773	428

Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of SEQ ID Nos. 11 to 30, 41 to 60, 71 to 90, 101 to 120, and 131 to 150.

In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are inserted, deleted and/or substituted with other nucleotides in SEQ ID Nos. 11 to 30, 41 to 60, 71 to 90, 101 to 120, and

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131 to 150 shall come within the scope of the present invention.

In a similar manner, any protein in which one or plural amino acids are inserted, deleted and/or substituted with other amino acids shall come within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by SEQ ID Nos. 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.

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The cDNAs of the present invention include cDNA fragments (10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or in the base sequences represented by SEQ ID Nos. 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

30 The polynucleotides provided by the present invention can be used by the research community for various purposes.

The polynucleotides can be used to express recombinant

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protein for analysis, characterization or therapeutic use: as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source information to derive PCR primers for fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodiesusing DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, example, that described in Gyuris et al., Cell 75:791-803 to identify polynucleotides encoding the protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine

levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

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Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be

18

administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

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A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular

Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

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Assays for proliferation and differentiation hematopoietic and lymphopoietic cells include, limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1991; Moreau et al., Nature 336:690-692, Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 -Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 John Wiley and Sons, Toronto. 1991; pp. 6.15.1 Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp.

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6.13.1, John Wiley and Sons, Toronto. 1991.

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Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, limitation, those described in: Current Protocols Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. 77:6091-6095, 1980; Weinberger et al., Eur. J. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512,

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial orfungal infections, or may result from autoimmune disorders. More specifically, infectious causes by viral, bacterial, fungal or infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp.

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and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

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Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. regulation may be in the form of inhibiting or blocking an already response in progress or may preventing the induction of an immune response. The functions of activated T cells may be inhibited suppressing T cell responses or by inducing tolerance in T cells, or both. Immunosuppression of T cell is responses generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigenspecific and persists after exposure to the tolerizing agent

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has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

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Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will useful in situations of tissue, skin and transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding Blocking costimulatory signal. В lymphocyte function in this matter prevents cytokine synthesis immune cells, such as T cells, and thus immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by lymphocyte antigen-blocking reagents may necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

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tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

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efficacy of particular blocking The in preventing organ transplant rejection or GVHD assessed using animal models that are predictive of efficacy Examples of appropriate systems which can be in humans. include allogeneic cardiac grafts in rats xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Iq fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antiqen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate Administration of reagents which block disease symptoms. costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating

24

autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune Examples include murine experimental autoimmune diseases. systemic lupus erythmatosis in MRL/lpr/lpr encephalitis, or NZB hybrid mice, murine autoimmune arthritis, diabetes mellitus in NOD mice and BB rats, and experimental myasthenia gravis (see Paul Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

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10 Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting 15 initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the commoncold, and encephalitis might be alleviated by the administration 20 of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the

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transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. tumor cells obtained from a example, patient can transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessarv costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and , microglobulin protein or an MHC class

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chain protein and an MHC class II chain protein to II thereby express MHC class I or MHC class II proteins on the Expression of the appropriate class I or cell surface. class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific Thus, the induction of a T cell mediated immune immunity. response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

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The activity of a protein of the invention may, among other means, be measured by the following methods:

thymocyte Suitable assays for or splenocyte cytotoxicity include, without limitation, those described Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Marqulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., 135:1564-1572, 1985; Takai et al., J. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J.

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Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

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Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Thl and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Interscience (Chapter 3, In Vitro assays for Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965,

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1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to

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stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes monocytes/macrophages (i.e., traditional activity) CSF useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting proliferation of growth and megakaryocytes consequently of platelets thereby allowing prevention treatment of various platelet disorders thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the abovementioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo conjunction with (i.e., in bone transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and

PCT/JP99/03929 WO 00/05367

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Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, 5 described Methylcellulose colony in: forming Freshney, M.G. In Culture of Hematopoietic Cells. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. 10 USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in presence of stromal cells, Spooncer, E., Dexter, M. Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

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A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is

not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

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A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of boneforming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or blocking inflammation or processes of destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and

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in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, differentiation of progenitors of tendonligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head

trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

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It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. W095/16035 (bone, cartilage, tendon);

WO 00/05367

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PCT/JP99/03929

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International Patent Publication No. W095/05846 (nerve, neuronal); International Patent Publication No. W091/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

10 A protein of the present invention may also exhibit activininhibin-related or activities. Inhibins characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). 15 Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female and decrease spermatogenesis in male mammals. 20 Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- group, may be useful as a fertility inducing therapeutic, based upon the 25 ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, 30 sheep and pigs.

The activity of a protein of the invention may, among

other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

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A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. example, attraction of lymphocytes, monocytes neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among

WO 00/05367 PCT/JP99/03929

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other means, be measured by the following methods:

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Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. 25: 1744-1748; Gruber et al. J. of 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (includinghereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

30 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include,

WO 00/05367 PCT/JP99/03929

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without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

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A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their (including without limitation, cellular adhesion molecules as selectins, integrins and their ligands) receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful screening of potential peptide or small inhibitors of the relevant receptor/ligand interaction. protein of the present invention (including, limitation, fragments of receptors and ligands) themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22),

WO 00/05367

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PCT/JP99/03929

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Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cellcell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory disease, Crohn's disease or resulting from over production of ytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A

protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

10 Other Activities

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A protein of the invention may also exhibit one or more following additional activities or inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body size or shape (such as, for example, augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or effecting the fertility of male or female subjects: effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of

WO 00/05367 PCT/JP99/03929

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embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

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The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic operations with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the manufacturer's instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: (1994)1.

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA library of fibrosarcoma cell line HT-1080 (WO98/11217), the cDNA library of osteosarcoma cell line Saos-2 (WO97/33993), the cDNA library of osteosarcoma cell line U-2 OS (WO98/21328), the cDNA library of epidermoid

carcinoma cell line KB (WO98/11217), the cDNA library of tissues of stomach cancer delivered by the (WO98/21328), the cDNA library of liver tissue delivered by the operation (WO98/21328), and were used for the cDNA libraries. Full-length cDNA clones were selected respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA consisting full-length of the CDNA hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. Any clone that has a hydrophobic region being putative as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

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The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [35]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 μ l containing 12.5 μ l μ of $T_{\nu}T$ reticulocyte lysate, 0.5 μ l of a buffer solution (attached to the kit), 2 μ l of an amino acid mixture (without methionine), 2 μ l of [35S]methionine (Amersham) (0.37 MBq/ μ l), 0.5 μ l of T7 RNA polymerase, and 20 U of RNasin. Also, an experiment in the presence of a membrane system was carried

WO 00/05367 PCT/JP99/03929

42

out by adding to this reaction system 2.5 μ l of a canine pancreas microsome fraction (Promega). To 3 μ l of the resulting reaction solution was added 2 μ l of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

(3) Expression by COS7

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Escherichia coli cells bearing the expression vector for the protein of the present invention was incubated at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing 100 μ g/ml of ampicillin, the helper phage M13K07 $(50 \mu 1)$ was added, and the incubation was continued at 37°C overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from simian kidney, COS7, were incubated at 37°C in the presence of 5% CO₂ in the Dulbecce's modified Eagle's culture medium (DMEM) containing 10% fetal calf serum. Into a 6-well plate (Nunc, well diameter: 3 cm) were inoculated with 1 x 10^5 COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO₂. After the culture medium was removed, the cell surface was washed with a phosphate buffer solution and then washed again with DMEM containing 50 mM Trishydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 μ l of the single-stranded phage suspension, 0.6 ml of the DMEM culture medium, and 3 μ l of

TRANSFECTAM™ (IBF) and the resulting mixture was incubated at 37°C for 3 hours in the presence of 5% CO2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the incubation was carried out at 37°C for 2 days in the presence of 5% CO2. After the culture medium was replaced by a culture medium [35S]cystine or [35S]methionine, the incubation was carried out for one hour. After the culture medium and the cells were separated by centrifugation, proteins in the culture medium fraction and the cell-membrane fraction were subjected to SDS-PAGE.

(4) Clone Examples <HP01550> (SEQ ID Nos. 1, 11, and 21)

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Determination of the whole base sequence of the cDNA insert of clone HP01550 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 65-bp 5'-untranslated region, a 378-bp ORF, and a 67-bp 3'untranslated region. The ORF codes for a protein consisting of 125 amino acid residues and there existed one putative domain. Figure 1 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 15 kDa that was almost identical with the molecular weight of 13,825 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis elegans hypothetical protein F45G2.c (GenBank Accession No. 293382). Table 2 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C.

elegans hypothetical protein F45G2.c (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 44.5% in the entire region.

Table 2

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA338859) in ESTS, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02593> (SEQ ID Nos. 2, 12, and 22)

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Determination of the whole base sequence of the cDNA insert of clone HP02593 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 103-bp 5'-untranslated region, a 396-bp ORF,

and a 198-bp 3'-untranslated region. The ORF codes for a protein consisting of 131 amino acid residues and there existed four putative transmembrane domains at the C-terminus. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to a human OB-R gene-related protein (EMBL Accession No. Y12670). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human OB-R gene-related protein (OB). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 67.9% in the entire region.

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Table 3

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OB GRGDDFSWEOW

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA306490) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10195> (SEQ ID Nos. 3, 13, and 23)

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Determination of the whole base sequence of the CDNA insert of clone HP10195 obtained from cDNA library of human fibrosarcoma HT-1080 revealed the structure consisting of a 286-bp 5'-untranslated region, a 729-bp ORF, and a 604-bp 3'-untranslated region. The ORF codes for a consisting of 242 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. vitro translation resulted in formation of a translation product of 32 kDa that was somewhat larger than the molecular weight of 27,300 predicted from the ORF. When expressed in COS7 cells, an expression product of about 21 observed in the supernatant fraction and the kDa was membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed the registration of sequences that were similar to the Aplysia VAP-33 (SWISS-PROT Accession No. P53173). Table 4 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Aplysia VAP-33 (AP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the

present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 46.5% in the entire region.

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Table 4

HP MAKHEQILVLDPPTDLKFKGPFTDVVTTNLKLRNPSDRKVCFKVKTTAPRRYCVRPNSGI AP MASHEOALILEPAGELRFKGPFTDVVTADLKLSNPTDRRICFKVKTTAPKRYCVRPNSGI 10 HP IDPGSTVTVSVMLOPFDYDPNEKSKHKFMVQTIFAPPNTSD-MEAVWKEAKPDELMDSKL AP LEPKTSIAVAVMLOPFNYDPNEKNKHKFMVOSMYAPDHVVESQELLWKDAPPESLMDTKL HP RCVFEMPNENDKLNDMEPSK-----AVPLNASKQDGPMPKP-HSVSLNDTE ***** 15 AP RCVFEMPDGSHOAPASDASRATDAGAHFSESALEDPTVASRKTETQSPKRVGAVGSAGED HP TRKLMEECKRLOGEMMKLSEENRHLRDEGLRLRKVAHSD--KPGSTSTASFRDNVTSPLP AP VKKLOHELKKAQSEITSLKGENSQLKDEGIRLRKVAMTDTVSPTPLNPSPAPAAAVRAFP 20 HP SLLVVIAAIFIGFFLGKFIL ... * **** . * . . . *** . * AP PVVYVVAAIILGLIIGKFLL

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA447905) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10423> (SEQ ID Nos. 4, 14, and 24)

PCT/JP99/03929

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Determination of the whole base sequence of the cDNA insert of clone HP10423 obtained from cDNA library of human line U-2 OS revealed the structure osteosarcoma cell consisting of a 64-bp 5'-untranslated region, a 795-bp ORF, and a 207-bp 3'-untranslated region. The ORF codes for a protein consisting of 264 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane domain at the N-terminus. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was almost identical with the molecular weight of 29,377 predicted from the ORF. When expressed in COS7 cells, an expression product of about 31 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D80116) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10506> (SEQ ID Nos. 5, 15, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP10506 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 53-bp 5'-untranslated region, a 339-bp ORF, and a 226-bp 3'-untranslated region. The ORF codes for a protein consisting of 112 amino acid residues and there existed one putative transmembrane domain. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

PCT/JP99/03929

49

Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,821 predicted from the ORF. When expressed in COS7 cells, an expression product of about 13 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA282544) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

15 <HP10507> (SEQ ID Nos. 6, 16, and 26)

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Determination of the whole base sequence of the cDNA insert of clone HP10507 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 412-bp 5'-untranslated region, a 441-bp ORF, and a 168-bp 3'untranslated region. The ORF codes for a protein consisting of 146 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane 6 depicts Figure C-terminus. domain at the hydrophobicity/hydrophilicity profile, obtained by the Kytepresent protein. Doolittle method, of the translation resulted in formation of a translation product of 19 kDa that was somewhat larger than the molecular weight of 16,347 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA424759) in ESTs, but, since they

WO 00/05367 PCT/JP99/03929

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are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

5 <HP10548> (SEQ ID Nos. 7, 17, and 27)

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Determination of the whole base sequence of the cDNA insert of clone HP10548 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 330-bp 5'-untranslated region, a 1035-bp ORF, and a 67-bp 3'untranslated region. The ORF codes for a protein consisting of 344 amino acid residues and there existed four putative transmembrane domains. Figure 7 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, the present protein. of translation resulted in formation of a translation product of a high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA143152) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

25 <HP10566> (SEQ ID Nos. 8, 18, and 28)

Determination of the whole base sequence of the cDNA insert of clone HP10566 obtained from cDNA library of the human stomach cancer revealed the structure consisting of a 61-bp 5'-untranslated region, a 294-bp ORF, and a 246-bp 3'-untranslated region. The ORF codes for a protein consisting of 97 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 8 depicts the

hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,452 predicted from the ORF. When expressed in COS7 cells, an expression product of about 12 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W79821) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10567> (SEQ ID Nos. 9, 19, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10567 obtained from cDNA library of the human stomach cancer revealed the structure consisting of a 77-bp 5'-untranslated region, a 375-bp ORF, and a 133-bp 3'untranslated region. The ORF codes for a protein consisting of 124 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kytepresent protein. In the Doolittle method, of translation resulted in formation of a translation product of 14 kDa that was almost identical with the molecular weight of 14,484 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA428475) in ESTs, but, since they

are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10568> (SEQ ID Nos. 10, 20, and 30)

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Determination of the whole base sequence of the cDNA insert of clone HP10568 obtained from cDNA library of the human stomach cancer revealed the structure consisting of a 56-bp 5'-untranslated region, a 984-bp ORF, and a 60-bp 3'untranslated region. The ORF codes for a protein consisting of 327 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane Figure 10 depicts C-terminus. the hydrophobicity/hydrophilicity profile, obtained by the Kytethe present protein. Doolittle method, of translation resulted in formation of a translation product of 36.5 kDa that was almost identical with the molecular weight of 34,326 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 40 kDa which is considered to have a sugar chain being In addition, there exist in the amino acid attached. sequence of this protein two sites at which N-glycosylation may occur (Asn-Leu-Thr at position 138 and Asn-Leu-Ser at position 206). Application of the (-3,-1) rule, a method for the secretory signal predicting the cleavage site of sequence, allows to expect that the mature protein starts from valine at position 24. When expressed in COS7 cells, an expression product of about 31 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was similar to the human cell-surface A33 antigen

(SWISS-PROT Accession No. Q99795). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human cell-surface A33 antigen (A3). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 30.0% in the N-terminal region of 243 residues.

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Table 5

HP MAELPGPFLCGALLGFLCLSGLAVEVKVPTEPLSTPLGKTAELTCTYSTSVGDSFAL-EW *..*..* . *... **...*. ** .*... .* .* MVGKMWPVLWTLCAVRVTVDAISVETPQDVLRASQGKSVTLPCTYHTSTSSREGLIOW 15 **A3** HP SFVQPGKPISESHPILYFTNGHLYPTGSKSKRVSLLQNPPTVGVATLKLTDVHPSDTGTY A3 DKLL--LTHTERVVIWPFSNKN-YIHGELYKNRVSISNNAEQSDASITIDQLTMADNGTY HP LCQVNNPPDFYTNGLGLINLTVLVPPSNPLCSQSGQTSVGGSTALRCSSSEGAPKPVYNW 20 A3 ECSVSLMSDLEGNTKSRVRLLVLVPPSKPECGIEGETIIGNNIQLTCQSKEGSPTPQYSW HP VRLGTFPTPSPGSMVQDEVSGQLILTNLSLTSSGTYRCVATNQMGSASCELTLSVTEPS-A3 KRYNILNOEOP--LAOPASGOPVSLKNISTDTSGYYICTSSNEEGTOFCNITVAVRSPSM HP -QGRVAGALIGVLLGVLLLSVAAFCLVRFQKERGKKPKETYGGSDLREDAIAPGISENTC 25 * ** ** A3 NVALYVGIAVGVVAALIIIGIIIYCCCCRGKDDNTEDKEDARPNREAYEEPPEQLRELSR HP MRADSSKGFLERPSSASTVTTTKSKLPMVV 30 A3 EREEEDDYRQEEQRSTGRESPDHLDQ

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration

PCT/JP99/03929

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of sequences that shared a homology of 90% or more (for example, Accession No. T24595) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01426> (SEQ ID Nos. 31, 41, and 51)

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Determination of the whole base sequence of the cDNA insert of clone HP01426 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 1-bp 5'-untranslated region, a 942-bp ORF, and a 122-bp 3'untranslated region. The ORF codes for a protein consisting of 313 amino acid residues and there existed a putative depicts Figure 11 signal. hydrophobicity/hydrophilicity profile, obtained by the Kytethe present protein. method, of translation resulted in formation of a translation product of 36 kDa that was almost identical with the molecular weight of 34,955 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 38 kDa which is considered to have a sugar chain being attached after secretion. In addition, there exists in the amino acid sequence of this protein one site at which Nglycosylation may occur (Asn-Ser-Ser at position 163). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from tryptophan at position 17. When expressed in COS7 cells, an expression product of about 39 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the

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protein was similar to the Xenopus laevis cortical granule lectin (EMBL Accession No. X82626). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the X. laevis cortical granule lectin (XL). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 67.9% in the region other than the N-terminal region.

Table 6

HP MNQLSFLLFLIATTRGWSTDEANTYFKEWTCSSSPSLPRSCKEIKDECPSAFDGLYFLRT ******* . * **.* * . 15 XL MLVHILLLVTGGLSQSCEPVVIVASKNMVKQLDCDKFRSCKEIKDSNEEAQDGIYTLTS HP ENGVIYQTFCDMTSGGGGWTLVASVHENDMRGKCTVGDRWSSQQGSKADYPEGDGNWANY * ******* *********** * **** XL SDGISYQTFCDMTTNGGGWTLVASVHENNMAGKCTIGDRWSSQQGNRADYPEGDGNWANY HP NTFGSAEAATSDDYKNPGYYDIQAKDLGIWHVPNKSPMQHWRNSSLLRYRTDTGFLQTLG 20 XL NTFGSAGGATSDDYKNPGYYDIEAYNLGVWHVPNKTPLSVWRNSSLQRYRTTDGILFKHG HP HNLFGIYQKYPVKYGEGKCWTDNGPVIPVVYDFGDAQKTASYYSPYGQREFTAGFVQFRV XL GNLFSLYRIYPVKYGIGSCSKDSGPTVPVVYDLGSAKLTASFYSPDFRSQFTPGYIQFRP 25 HP FNNERAANALCAGMRVTGCNTEHHCIGGGGYFPEASPQQCGDFSGFDWSGYGTHVGYSSS XL INTEKAALALCPGMKMESCNVEHVCIGGGGYFPEADPRQCGDFAAYDFNGYGTKKFNSAG HP REITEAAVLLFYR ****** 30 XL IEITEAAVLLFYL

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R06009) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02515> (SEQ ID Nos. 32, 42, and 52)

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Determination of the whole base sequence of the cDNA insert of clone HP02515 obtained from cDNA library of human line Saos-2 revealed the cell osteosarcoma consisting of a 176-bp 5'-untranslated region, a 690-bp ORF, and a 71-bp 3'-untranslated region. The ORF codes for a protein consisting of 229 amino acid residues and there existed a putative secretory signal at N-terminus and one putative transmembrane domain at the C-terminus. Figure 12 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation 27 kDa that was almost identical with the molecular weight of 26,000 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 25.5 kDa from which the secretory signal is considered to have been cleaved. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from phenylalanine at position 28.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human T1/ST2 receptor binding protein (GenBank Accession No. U41804). Table 7 shows the

comparison between amino acid sequences of the human protein of the present invention (HP) and the human T1/ST2 receptor binding protein (T1). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 55.8% in the entire region.

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Table 7

T1 AFEARDRNLOEGNLERVNFWSAVNVAVLLLVAVLQVCTLKRFFQDKRPVPT

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA381943) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02575> (SEQ ID Nos. 33, 43, and 53)

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Determination of the whole base sequence of the cDNA insert of clone HP02575 obtained from cDNA library of human osteosarcome cell line Saos-2 revealed the consisting of a 55-bp 5'-untranslated region, a 1404-bp ORF, and a 219-bp 3'-untranslated region. The ORF codes for a protein consisting of 467 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 13 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 52 kDa that was almost identical with the molecular weight of 54,065 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 57 kDa which is considered to have a sugar chain being attached afetr secretion. In addition, there exist in the amino acid sequence of this protein three sites at which N-glycosylation may occur (Asn-Arg-Thr at position 171, Asn-Ser-Thr at position 239 and Asn-Asp-Thr at position rule, a method Application of the (-3,-1)predicting the cleavage site of the secretory sequence, allows to expect that the mature protein starts from histidine at position 29. When expressed in COS7 cells, an expression product of about 55 kDa was observed in the supernatant fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human α -L-fucosidase (SWISS-PROT Accession No. P04066). Table 8 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human α -L-fucosidase (FC). Therein,

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the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 54.8% in the entire region.

Table 8

	HP	${\tt MRPQELPRLAFPLLLLLLLLPPPPC-PAHSATRFDPTWESLDARQLPAWFDQAKFGIFI}$
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	FC	MRSRPAGPALLLLLLFLGAAESVRRAQPPRRYTPDWPSLDSRPLPAWFDEAKFGVFI
	HP	${\tt HWGVFSVPSFGSEWFWWYWQKEKIPKYVEFMKDNYPPSFKYEDFGPLFTAKFFNANQWAD}$
		******** ****** * * * * * * * * * * * *
	FC	${\tt HWGVFSVPAWGSEWFWWHWQGEGRPQYQRFMRDNYPPGFSYADFGPQFTARFFHPEEWAD}$
15	HP	${\tt IFQASGAKYIVLTSKHHEGFTLWGSEYSWNWNAIDEGPKRDIVKELEVAIRNRTDLRFGL}$
		*** *** *** *** *** * * * * *** * * * *
	FC	${\tt LFQAAGAKYVVLTTKHHEGFTNWPSPVSWNWNSKDVGPHRDLVGELGTALRKR-NIRYGL}$
	HP	$\verb"YYSLFEWFHPLFLEDESSSFHKRQFPVSKTLPELYELVNNYQPEVLWSDGDGGAPDQYWN"$
		*.**.****** *** .**.**.**.**.**.*
20	FC	$\verb YHSLLEWFHPLYLLDKKNGFKTQHFVSAKTMPELYDLVNSYKPDLIWSDGEWECPDTYWN $
	HP	${\tt STGFLAWLYNESPVRGTVVTNDRWGAGSICKHGGFYTCSDRYNPGHLLPHKWENCMTIDK}$
		..***.** * * * * * * * * * * * * *
	FC	STNFLSWLYNDSPVKDEVVVNDRWGQNCSCHHGGYYNCEDKFKPQSLPDHKWEMCTSIDK
	HP	LSWGYRREAGISDYLTIEELVKQLVETVSCGGNLLMNIGPTLDGTISVVFEERLRQMGSW
25		****** * * * * . * . *
	FC	FSWGYRRDMALSDVTEESEIISELVQTVSLGGNYLLNIGPTKDGLIVPIFQERLLAVGKW
	HP	LKVNGEAIYETHTWRSQNDTVTPDVWYTSKPKEKLVYAIFLKWPTSGQLFLGHPKAILGA
		********* * ****** ******.** * * *
	FC	LSINGEAIYASKPWRVQWEKNTTSVWYTSKGSAVYAIFLHWPENGVLNLESPITT-ST
30	HP	TEVKLLGHGQPLNWISLEQNGIMVELPQLTIHQMPCKWGWALALTNVI
		*** *.********
	FC	TKITMLGIQGDLKWSTDPDKGLFISLPQLPPSAVPAEFAWTIKLTGVK

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N28668) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10357> (SEQ ID Nos. 34, 44, and 54)

Determination of the whole base sequence of the cDNA insert of clone HP10357 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 113-bp 5'-untranslated region, a 300-bp ORF, and a 54-bp 3'untranslated region. The ORF codes for a protein consisting of 99 amino acid residues and there existed two putative Figure 14 depicts domains. transmembrare hydrophobicity/hydrophilicity profile, obtained by the Kyteprotein. Doolittle method, of the present translation resulted in formation of a translation product of 11 kDa that was almost identical with the molecular weight of 10,923 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA477156) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10447> (SEQ ID Nos. 35, 45, and 55)

Determination of the whole base sequence of the cDNA

insert of clone HP10447 obtained from cDNA library of human liver revealed the structure consisting of a 271-bp 5'-570-bp ORF, and a 34-bp untranslated region, a untranslated region. The ORF codes for a protein consisting of 189 amino acid residues and there existed five putative domains. Figure 15 depicts transmembrare hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA296976) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10477> (SEQ ID Nos. 36, 46, and 56)

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Determination of the whole base sequence of the cDNA insert of clone HP10477 obtained from cDNA library of human liver revealed the structure consisting of a 149-bp 5'-untranslated region, a 1092-bp ORF, and a 15-bp 3'-untranslated region. The ORF codes for a protein consisting of 363 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 16 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 40 kDa that was almost identical with the molecular weight of 39,884 predicted from the ORF.

The search of the protein data base using the amino

acid sequence of the present protein revealed that the protein was similar to the human peptidoglycan recognition protein (GenBank Accession No. AF076483). Table 9 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human peptidoglycan recognition protein (PG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 54.8% in the entire region.

Table 9

HP MVDSLLAVTLAGNLGLTFLRGSQTQSHPDLGTEGCWDQLSAPRTFTLLDPKASLLTKAFL 15 HP NGALDGVILGDYLSRTPEPRPSLSHLLSQYYGAGVARDPGFRSNFRRQNGAALTSASILA HP QOVWGTLVLLORLEPVHLQLOCMSQEQLAQVAANATKEFTEAFLGCPAIHPRCRWGAAPY MSRRSMLLAWALPSLLRLGAAQETEDPACCSPIVPRNEWKALA-PG 20 HP RGRPKLLQLPLGFLYVHHTYVPAPPCTDFTRCAANMRSMQRYHQDTQGWGDIGYSFVVGS PG SECAOHLSLPLRYVVVSHT--AGSSCNTPASCQQQARNVQHYHMKTLGWCDVGYNFLIGE HP DGYVYEGRGWHWVGAHTLGH-NSRGFGVAIVGNYTAALPTEAALRTVRDTLPSCAVRAGL ** ****** PG DGLVYEGRGWNFTGAHSGHLWNPMSIGISFMGNYMDRVPTPQAIRAAQGLL-ACGVAQGA 25 HP LRPDYALLGHRQLVRTDCPGDALFDLLRTWPHFTATVKPRPARSVSKRSRREPPPRTLPA **..*.* ***.. ** .**..*..*** PG LRSNYVLKGHRDVORTLSPGNOLYHLIONWPHYRSP

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration

of sequences that shared a homology of 90% or more (for example, Accession No. AA424759) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10513> (SEQ ID Nos. 37, 47, and 57)

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Determination of the whole base sequence of the cDNA insert of clone HP10513 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 134-bp 5'-untranslated region, a 750-bp ORF, and a 0-bp 3'-untranslated region. The ORF codes for a protein consisting of 249 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 17 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 29 kDa that was almost identical with the molecular weight of 27,373 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human hypothetical protein KIAA0512 (GenBank Accession No. AB011084). Table 10 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human hypothetical protein KIAA0512 (KI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 31.6% in the C-terminal region of 196 amino acid residues.

WO 00/05367

PCT/JP99/03929

64

Table 10

HP MGGPRGAGWVAAGLLLGAGACYCIYRLTRGRRRG 5 KI RGRGRRPVAMQKRPFPYEIDEILGVRDLRKVLALLQKSDDPFIQQVALLTLSNNANYSCN HP DRELGIRSSKSAEDLTDGSYDDVLNAEQLQKLLYLLESTEDPVIIERALITLGNNAAFSV KI QETIRKLGGLPIIANMINKTDPHIKEKALMAMNNLSENYENQGRLQVYMNKVMDDIMASN 10 HP NQAIIRELGGIPIVANKINHSNQSIKEKALNALNNLSVNVENQIKIKVQVLKLLLNLSEN KI LNSAVQVVGLKFLTNMTITNDYQHLLVNSIANF--FRLLSQGGGKIKVEILKILSNFAEN HP PAMTEGLLRAQVDSSFLSLYDSHVAKEILLRVLTLFQNIKNCLKIEGHLAVQPTFTEGSL *.* . **..** .** ***.*...***. * . *. * 15 KI PDMLKKLLSTQVPASFSSLYNSYVESEILINALTLFEIIYDNLRAE--VFNYREFNKGSL HP FFL-LHGEECAQKIRALVDHHDAEVKEKVVTIIPKI *.* .. *..****..*** ** **... *. KI FYLCTTSGVCVKKIRALANHHDLLVKVKVIKLVNKF

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N92228) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10540> (SEQ ID Nos. 38, 48, and 58)

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Determination of the whole base sequence of the cDNA insert of clone HP10540 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure

WO 00/05367

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PCT/JP99/03929

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consisting of a 47-bp 5'-untranslated region, a 297-bp ORF, and a 245-bp 3'-untranslated region. The ORF codes for a protein consisting of 98 amino acid residues and there existed two putative transmembrane domains. Figure 18 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein similar was to the Caenorhabditis hypothetical protein CEF49C12.12 (GenBank Accession Z68227). Table 11 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein CEF49C12.12 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 36.1% in the entire region.

Table 11

CE MGKICPLMGPKMSAFCMVMSVWGVIFLGLLGVFFYIQAVTLFPDLHF-EGHGKVPSSVID HP NLYEQVSYNCFIAAGLYLLLGGFSFCQVRLNKRKEYMVR

^{* * ***** * * **}

³⁰ CE AKYNEKATQCWIAAGLYAVTLIAVFWQ---NKYNTAQIF

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA420715) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

10 <HP10557> (SEQ ID Nos. 39, 49, and 59)

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Determination of the whole base sequence of the cDNA insert of clone HP10557 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 24-bp 5'-untranslated region, a 519-bp ORF, and a 130-bp 3'untranslated region. The ORF codes for a protein consisting of 172 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 19 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 32 kDa that was larger than the molecular weight of 18,844 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 39 kDa is considered to have been subjected to modification after secretion. In addition, there exist in the amino acid sequence of this protein no site at which Nglycosylation may occur. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glycine at position 32. When expressed in COS7 cells, an expression product of about 20 kDa was observed in the supernatant fraction and the membrane fraction.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human progesterone binding protein (EMBL Accession No. AJ002030). Table 12 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human progesterone binding protein (PG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 30.5% in the C-terminal region of 151 amino acid residues.

Table 12

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

WO 00/05367 PCT/JP99/03929

68

example, Accession No. AA101709) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10563> (SEQ ID Nos. 40, 50, and 60)

Determination of the whole base sequence of the cDNA insert of clone HP10563 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 126-bp 5'-untranslated region, a 363-bp ORF, and a 936-bp 3'-untranslated region. The ORF codes for a protein consisting of 120 amino acid residues and there existed two putative transmembrane domains. Figure 20 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 18.5 kDa that was larger than the molecular weight of 13,180 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana hypothetical protein F27F23.15 (GenBank Accession No. AC003058). Table 13 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the A. thaliana hypothetical protein F27F23.15 (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.5% in the entire region.

PCT/JP99/03929

WO 00/05367

Table 13

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HP MMPSRTNLATGIPSSKVKYSRLSSTDDGYIDLQFKKTPPKIPYKAIALATVLFLIGAFLI

.. *... * *.*.*. *...*. *

AT MAYVDHAFSISDEDLMIGTSY-TVSNRPPVKEISLAVGLLVFGTLGI

HP IIGSLLLSGYISKGGADRAVPVLIIGILVFLPGFYHLRIAYYASKGYRGYSYDDIPDFDD

AT VLGFFMAYNRVG-GDRGHGIFFIVLGCLLFIPGFYYTRIAYYAYKGYKGFSFSNIPSV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA083574) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01467> (SEQ ID Nos. 61, 71, and 81)

Determination of the whole base sequence of the cDNA insert of clone HP01467 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 65-bp 5'-untranslated region, a 924-bp ORF, and a 447-bp 3'-untranslated region. The ORF codes for a protein consisting of 307 amino acid residues and there existed three putative transmembrane domains. Figure 21 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino

acid sequence of the present protein revealed that the protein was similar to the rat Sec22 homologue (GenBank Accession No. U42209). Table 14 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat Sec22 homologue (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 94.6% in the N-terminal region of 241 amino acid residues. The protein of the present invention was longer by 53 amino acids at the C-terminus than the rat Sec22 homologue.

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Table 14

HP MSMILSASVIRVRDGLPLSASTDYEQSTGMQECRKYFKMLSRKLAQLPDRCTLKTGHYNI ********************** RN MSMILSASVVRVRDGLPLSASTDCEQSAGVQECRKYFKMLSRKLAQFPDRCTLKTGRHNI 20 HP NFISSLGVSYMMLCTENYPNVLAFSFLDELQKEFITTYNMMKTNTAVRPYCFIEFDNFIQ *************** RN NFISSLGVSYMMLCTENYPNVLAFSFLDELQKEFITTYNMMKTNTAVRPYCFIEFDNFIO HP RTKQRYNNPRSLSTKINLSDMQTEIKLRPPYQISMCELGSANGVTSAFSVDCKGAGKISS *************** 25 RN RTKQRYNNPRSLSTKINLSDMQMEIKLRPPYQIPMCELGSANGVTSAFSVDCKGAGKISS HP AHQRLEPATLSGIVGFILSLLCGALNLIRGFHAIESLLQSDGDDFNYIIAFFLGTAACLY ********* RN AHQRLEPATLSGIVAFILSLLCGALNLIRGFHAIESLLQSDGEDFSYMIAFFLGTAACLY HP QCYLLVYYTGWRNVKSFLTFGLICLCNMYLYELRNLWQLFFHVTVGAFVTLQIWLRQAQG

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RN QMICLCLOGRKERT

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA421925) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01956> (SEQ ID Nos. 62, 72, and 82)

Determination of the whole base sequence of the cDNA insert of clone HP01956 obtained from cDNA library of human liver revealed the structure consisting of a 86-bp region, a 552-bp ORF, and a 359-bp untranslated untranslated region. The ORF codes for a protein consisting of 183 amino acid residues and there existed one putative 22 transmembrane domain. Figure depicts the hydrophobicity/hydrophilicity profile, obtained by the Kytemethod. of the present protein. translation resulted in formation of a translation product of 20.5 kDa that was almost identical with the molecular weight of 20,073 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the yeast hypothetical protein 21.5 kDa (SWISS-PROT Accession No. P53073). Table 15 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the yeast hypothetical protein 21.5 kDa (SC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology

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of 34.3% in the C-terminal region of 108 amino acid residues.

Table 15

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA159753) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02545> (SEQ ID Nos. 63, 73, and 83)

Determination of the whole base sequence of the cDNA insert of clone HP02545 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 133-bp 5'-untranslated region, a 984-bp ORF, and a 636-bp 3'-untranslated region. The ORF codes for a

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protein consisting of 327 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 23 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the rat embigin (EMBL Accession No. AJ009698). Table 16 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat embigin (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 65.4% in the entire region.

PCT/JP99/03929

74

Table 16

HP MRALPGLLEARARTPRLLLLQCLLAAARPSSADGSAPDSPFTSPPLREEIMAN--NFSLE 5 RN MRSHTGLRALVAPGCSLLLL-YLLAATRPDRAVGDPADSAFTSLPVREEMMAKYANLSLE HP SHNISLTEHSSMPVEKNITLERPSNVNLTCQFTTSGDLNAVNVTWKKDGEQLE--NNYLV ..******.... *.*******...*. ..*. ..*. ..*. ..*. ..* RN TYNISLTEQTRVS-EQNITLERPSHLELECTFTATEDVMSMNVTWKKDDALLETTDGFNT HP SATGSTLYTQYRFTIINSKQMGSYSCFFREEKEQRGTFNFKVPELHGKNKPLISYVGDST 10 *.***.****...*****...** RN TKMGDTLYSQYRFTVFNSKQMGKYSCFLGEE--LRGTFNIRVPKVHGKNKPLITYVGDST HP VLTCKCQNCFPLNWTWYSSNGSVKVPVGVQM-NKYVINGTYANETKLKITQLLEEDGESY **.*.******* RN VLKCECQNCLPLNWTWYMSNGTAQVPIDVHVNDKFDINGSYANETKLKVKHLLEEDGGSY 15 HP WCRALFQLGESEEHIELVVLSYLVPLKPFLVIVAEVILLVATILLCEKYTQKKKKHSDEG **** *.***** *.**** ***** *. ****** *. ***** ***** ***** RN WCRAAFPLGESEEHIKLVVLSFMVPLKPFLAIIAEVILLVAIILLCEVYTQKKKNDPDDG HP KEFEQIEQLKSDDSNGIENNVPRHRKNESLGQ ******* 20 RN KEFEQIEQLKSDDSNGIENNVPRYRKTDSGDQ

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA312629) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP02551> (SEQ ID Nos. 64, 74, and 84)

Determination of the whole base sequence of the cDNA insert of clone HP02551 obtained from cDNA library of human

line Saos-2 revealed the osteosarcoma cell consisting of a 61-bp 5'-untranslated region, a 672-bp ORF, and a 384-bp 3'-untranslated region. The ORF codes for a protein consisting of 223 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 24 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was somewhat larger than the molecular weight of 24,555 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 26 kDa from which the secretory signal is considered to have been cleaved. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamine at position 20.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse FGF binding protein (GenBank Accession No. U49641). Table 17 shows comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse FGF binding protein (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 21.2% in the entire region other than the N-terminal region. In particular, all the eight cysteine residues contained in the both proteins were conserved.

Table 17

	HP	MKFVPCLLLVTLSCLGTLGQAPRQKQGST
		••**• • •* • •••
5	MM	MRLHSLILLSFLLLATQAFSEKVRKRAKNAPHSTAEEGVEGSAPSLGKAQNKQRSRTSKS
	HP	GEEFHFQTGGRDSCTMRPSSLGQGAGEVWLRVDCRNTDQTYWCEYRGQPSMCQAFAADPK

	MM	LTHGKFVTKDQATCRWAVTEEEQGISLKVQCTQADQEFSCVFAGDPTDCLKHDKD-Q
	HP	SYWNQALQELRRLHHACQGA-PVLRPSVCREAGPQAHMQQVTSSLKGSPEPNQQPEAGTP
10		**.*** ** .** * * * * *
	MM	IYWKQVARTLRKQKNICRDAKSVLKTRVCRKRFPESNLKLVNPNARGNTKPRKEKAEVSA
	ΗP	SLRPKATVKLTEATQLGKDSMEELGKAKPTTRPTAKPTQPGPRPGGNEEAKKKAWEHCWK
		* * *. * . *. *. * * *
	MM	REHNKVQEAVSTEPNRIKEDI-TLNPAATQTM-TIRDPECLEDPDVLNQ-RKTALEFCGE
15	HP	PFQALCAFLISFFRG
	MM	SWSSICTFFLNMLQATSC

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA317400) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02631> (SEQ ID Nos. 65, 75, and 85)

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Determination of the whole base sequence of the cDNA insert of clone HP02631 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 42-bp 5'-untranslated region, a 147-bp ORF,

and a 1191-bp 3'-untranslated region. The ORF codes for a protein consisting of 48 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 25 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa or less.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA156969) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP02632> (SEQ ID Nos. 66, 76, and 86)

Determination of the whole base sequence of the cDNA insert of clone HP02632 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 50-bp 5'-untranslated region, a 1116-bp ORF, and a 337-bp 3'-untranslated region. The ORF codes for a protein consisting of 371 amino acid residues and there existed eight putative transmembrane domains. Figure 26 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis elegans hypothetical protein CELC2H12 (GenBank Accession No. U23169). Table 18 shows the comparison between amino acid sequences

78

of the human protein of the present invention (HP) and the C. elegans hypothetical protein CELC2H12 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 51.4% in the entire region.

Table 18

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	HP	MAWTKYQLFLAGLMLVTGSINTLSAKWADNFMAEGCGGSKEHSFQHPFLQAVGMFLGEFS
		* ***** ** ** ***** ** ** ****
	CE	MVAFAVIISVMMVVTGSLNTICAKWADSIKADGVPFNHPFLQATCMFFGEFL
	HP	CLAAFYLLRCRAAGQSDSSVDPQQPFNPLLFLPPALCDMTGTSL
15		***.*
	CE	CLVVFFLIFGYKRYVWNRANVQGESGSVTEITSEEKPTLPPFNPFLFFPPALCDILGTSI
	HP	MYVALNMTSASSFQMLRGAVIIFTGLFSVAFLGRRLVLSQWLGILATIAGLVVVGLADLL
		****.*.**.**
	CE	MYIGLNLTTASSFQMLRGAVIIFTGLLSVGMLNAQIKPFKWFGMLFVMLGLVIVGVTDIY
20		SKHDSQHKLSEVITGDLLIIMAQIIVAIQMVLEEKFVYKHNVHPLRAVGTEGLFGFVILS
		··*· ·· · · · · · · · · · · · · · · · ·
	CE	YDDDPLDDKNAIITGNLLIVMAQIIVAIQMVYEQKYLTKYDVPALFAVGLEGLFGMVTLS
		LLLVPMYYIPAG-SFSGNPRGTLEDALDAFCQVGQQPLIAVALLGNISSIAFFNFAGISV
		.**.*****.** * ***. *
25	CE	ILMIPFYYIHVPRTFSTNPEGRLEDVFYAWKEITEEPTIALALSGTVVSIAFFNFAGVSV
	HP	TKELSATTRMVLDSLRTVVIWALSLALGWEAFHALQILGFLILLIGTALYNGLHRPLLGR
	i	******************************
	CE	TKELSATTRMVLDSVRTLVIWVVSIPLFHEKFIAIQLSGFAMLILGTLIYNDILIGPWFR
		LSRGRPLAEESEQERLLGGTRTPINDAS
30	112	DSKGKFLAEESEQERULGGTKTPINDAS
o U		
	CE	RNILPNLSSHANCARCWLCICGGDSELIEYEQEDQEHLMEA

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N50907) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10488> (SEQ ID Nos. 67, 77, and 87)

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Determination of the whole base sequence of the cDNA insert of clone HP10488 obtained from cDNA library of human liver revealed the structure consisting of a 39-bp 5'-untranslated region, a 273-bp ORF, and a 421-bp 3'-untranslated region. The ORF codes for a protein consisting of 90 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 27 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 10,151 predicted from the ORF. When expressed in COS7 cells, an expression product of about 6 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H73534) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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Determination of the whole base sequence of the cDNA insert of clone HP10538 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the consisting of a 357-bp 5'-untranslated region, a 1500-bp ORF, and a 1911-bp 3'-untranslated region. The ORF codes for a protein consisting of 499 amino acid residues and there existed at least four putative transmembrane domains. Figure hydrophobicity/hydrophilicity profile, 28 depicts the obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse pore-forming K⁺ channel subunit (GenBank Accession No. AF056492). Table 19 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse pore-forming K⁺ channel subunit (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 32.4% in the N-terminal region of 241 amino acid residues.

Table 19

HP MVDRGPLLTSAIIFYLAIGAAIFEVLEEPHWKEAKKNYYTQKLHLLKEFPCLGQEGLDK ***. ** .*..** ..*.*. . . . * . . * * . . * . . * . . * . . 5 MM MRSTTLLALLALVLLYLVSGALVFQALEQPHEQQAQKKMDHGRDQFLRDHPCVSQKSLED HP ILEVVSDAAGQG-----VAITGNQTFNNWNWPNAMIFAATVITTIGYGNVAPKTPAGRLF ***** MM FIKLLVEALGGGANPETSWTNSSNHSSAWNLGSAFFFSGTIITTIGYGNIVLHTDAGRLF HP CVFYGLFGVPLCLTWISALGKFFGGRAKR----LGQFLTKRGVSLRKAQITCTVIFIVWG 10 *.**.* *.***. .*.. .* *. *. MM CIFYALVGIPLFGMLLAGVGDRLGSSLRRGIGHIEAIFLKWHVPPGLVRSLSAVLFLLIG HP VLVHLVIPPFVFMVTEGWNYIEGLYYSFITISTIGFGDFVAGVNPSANYHALYRYFVELW MM CLLFVLTPTFVFSYMESWSKLEAIYFVIVTLTTVGFGDYVPG-DGTGQNSPAYQPLVWFW 15 HP IYLGLAWLSLFVNWKVSMFVEVHKAIKKRRRRRKESFESSPHSRKALQVKGSTASKDVNI * .***... MM ILFGLAYFASVLTTIGNWLRAVSRRTRAEMGGLTAQAASWTGTVTARVTQRTGPSAPPPE

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R25184) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10542> (SEQ ID Nos. 69, 79, and 89)

Determination of the whole base sequence of the cDNA insert of clone HP10542 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 23-bp 5'-untranslated region, a 321-bp ORF, and a 426-bp 3'-

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untranslated region. The ORF codes for a protein consisting of 106 amino acid residues and there existed one putative transmembrane domain. Figure 29 the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,724 predicted from the ORF. When expressed in COS7 cells, an expression product of about 13 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA029683) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10571> (SEQ ID Nos. 70, 80, and 90)

20 Determination of the whole base sequence of the cDNA insert of clone HP10571 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 95-bp 5'-untranslated region, a 459-bp ORF, and a 675-bp 3'untranslated region. The ORF codes for a protein consisting 25 of 152 amino acid residues and there existed one putative transmembrane domain. Figure 30 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product 30 of 20 kDa that was larger than the molecular weight of 17,062 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 23 kDa

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which is considered to have a sugar chain being attached after secretion. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Ile-Thr at position 10).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA105822) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01470> (SEQ ID Nos. 91, 101, and 111)

Determination of the whole base sequence of the cDNA insert of clone HP01470 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 157-bp 5'-untranslated region, a 1077-bp ORF, and a 385-bp 3'untranslated region. The ORF codes for a protein consisting of 358 amino acid residues and there existed one putative transmembrane domain. Figure 31 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 43 kDa that was somewhat larger than the molecular weight of 40,489 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 40 kDa from which the secretory signal is considered to have been cleaved and a product of 43.5 kDa which is considered to have been subjected to some modification. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glycine at position 23. When

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expressed in COS7 cells, an expression product of about 44 kDa was observed in the supernatant fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the was similar to the Caenorhabditis hypothetical protein 39.9 kDa (SWISS-PROT Accession No. Q10005). Table 20 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein 39.9 kDa (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 58.9% in the entire region.

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PCT/JP99/03929

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Table 20

HP MAPONLSTFCLLLLYLIGAVIAGRDFYKILGVPRSASIKDIKKAYRKLALQLHPDRNPDD 5 CE MRILNVSLLVLASSLVAFVECGRDFYKILGVAKNANANQIKKAYRKLAKELHPDRNODD HF PQAQEKFQDLGAAYEVLSDSEKRKQYDTYGEEGL--KDGHQSSHGDIFSHFFGDFGFMFG *.*****..****** CE EMANEKFQDLSSAYEVLSDKEKRAMYDRHGEEGVAKMGGGGGGGHDPFSSFFGDF-FG-G HP GTPRQQDRNIPRGSDIIVDLEVTLEEVYAGNFVEVVRNKPVARQAPGKRKCNCRQEMRTT 10 . ..*.*.*. ** *******. *.*.*. *.*. *.*. *.*. *.*. *.*. CE GGGHGGEEGTPKGADVTIDLFVTLEEVYNGHFVEIKRKKAVYKQTSGTRQCNCRHEMRTE HP QLGPGRFQMTQEVVCDECPNVKLVNEERTLEVEIEPGVRDGMEYPFIGEGEPHVDGEPGD CE QMGQGRFQMFQVKVCDECPNVKLVQENKVLEVEVEVGADNGHQQIFHGEGEPHIEGDPGD 15 HP LRFRIKVVKHPIFERRGDDLYTNVTISLVESLVGFEMDITHLDGHKVHISRDKITRPGAK *.*.*. *** ***.******** ... ***** * **** * .. ***.*. CE LKFKIRIQKHPRFERKGDDLYTNVTISLQDALNGFEMEIQHLDGHIVKVQRDKVTWPGAR HP LWKKGEGLPNFDNNNIKGSLIITFDVDFPKEQLTEEAREGIKQLLKQGSVQ-KVYNGLOG 20 CE LRKKDEGMPSLEDNNKKGMLVVTFDVEFPKTELSDEQKAQIIEILQQNTVKPKAYNGL

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA282838) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

30 <HP002419> (SEQ ID Nos. 92, 102, and 112)

Determination of the whole base sequence of the cDNA insert of clone HP02419 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 253-bp

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5'-untranslated region, a 681-bp ORF, and a 1120-bp 3'untranslated region. The ORF codes for a protein consisting of 226 amino acid residues and there existed four putative transmembrane domains. Figure 32 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human hypothetical protein KIAA0108 (SWISS-PROT Accession No. Q15012). Table 21 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human hypothetical protein KIAA0108 (KI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.9% in the entire region.

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Table 21

MKMVAPWTRFYSNSCCLCCHVRTGTILLGVWYLIINAVVLLILLSALADPD---OY HP ****..** ************* 5 KI MVSMSFKRNRSDRFYSTRCCGCCHVRTGTIILGTWYMVVNLLMAILLTVEVTHPNSMPAV HP NFSSSELGGDFEF-MDDANMCIAIAISLLMILICAMATYGAYKQRAAWIIPFFCYOIFDF KI NIQYEVIGNYYSSERMADNACVLFAVSVLMFIISSMLVYGAISYQVGWLIPFFCYRLFDF HP ALNMLVAITVLIYPNSIQEYIRQLPPNFPYRDDVMSVNPTCLVLIILLFISIILTFKGYL 10 KI VLSCLVAISSLTYLPRIKEYLDQL-PDFPYKDDLLALDSSCLLFIVLVFFALFIIFKAYL HP ISCVWNCYRYINGRNSSDVLVYVT-SNDTTVLLPPYDDATVNGAAKEPPPPYVSA *.*****.**.** KI INCVWNCYKYINNRNVPEIAVYPAFEAPPQYVLPTY-EMAVKMPEKEPPPPYLPA 15

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA173214) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02631> (SEQ ID Nos. 93, 103, and 113)

Determination of the whole base sequence of the cDNA insert of clone HP02631 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 42-bp 5'-untranslated region, a 588-bp ORF, and a 750-bp 3'-untranslated region. Although the 49th amino acid residue is encoded by a stop codon, it is likely that this codon encodes selenocysteine from the molecular weight

of the translation product and the sequence comparison data with the Caenorhabditis elegans homologue. The ORF codes for a protein consisting of 195 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the intermediate region. Figure 33 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 58 kDa. In this case, the addition of a microsome led to the formation of a product of 56 kDa from which the secretory signal is considered to have been cleaved. Since both of these products are larger than the molecular weight of 22 kDa predicted from the ORF, it is likely that the protein interacts with another protein.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis elegans hypothetical protein C35C5.3 (EMBL Accession No. Z78417). Table 22 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein C35C5.3 (CE). U at position 49 in the amino acid sequence of the protein of the present invention represents selenocysteine. Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.9% in the entire region other than the Nterminal region. Cystein was found in the sequence of the C. elegans protein at the posistion corresponding to position 49 encoded by the stop codon (selenocysteine) of the protein of the present invention.

PCT/JP39/03929

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Table 22

HP MRLLLL 5 CE MRIHDELQKQDMSRFGVFIIGVLFFMSVCDVLRTEEHSHDENHVHEKDDFEAEFGDETDS HP LLVAASAMVRSEASANLGGVPSKRLKMQYATGPLLKFQICVSUGYRRVFEEYMRVISORY * *.. *** **...* CE QSFSQGTEEDHIEVREQSSFVKPTAVHHAKDLPTLRIFYCVSCGYKQAFDQFTTFAKEKY HP PDIRIEGENYLPQPIYRHIASFLSVFKLVLIGLIIVGKDPFAFFGMQAPSIWQWGQENKV 10 ..* ** *... * .** .** . * * * . . ** CE PNMPIEGANFAPVLWKAYVAQALSFVKMAVLVLVLGGINPFERFGLGYPQILQHAHGNKM HP YACMMVFFLSNMIENQCMSTGAFEITLNDVPVWSKLESGHLPSMQQLVQILDNEMKLNVH *********** CE SSCMLVFMLGNLVEQSLISTGAFEVYLGNEQIWSKIESGRVPSPQEFMQLIDAQLAVLGK 15 HP MDSIPHHRS CE APVNTESFGEFQQTV

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA156969) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02695> (SEQ ID Nos. 94, 104, and 114)

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Determination of the whole base sequence of the cDNA insert of clone HP02695 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 112-bp 5'-untranslated region, a 1020-bp ORF, and a 160-bp 3'-

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PCT/JP99/03929

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untranslated region. The ORF codes for a protein consisting of 339 amino acid residues and there existed three putative transmembrane domains. Figure 34 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 38 kDa that was almost identical with the molecular weight of 38,274 kDa predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the rat hypertension-induced protein S-2 fragment (PIR Accession No. 539959). Table 23 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat hypertension-induced protein S-2 fragment (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 74.3% in the entire region.

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Table 23

HP MNWELLLWLLVLCALLLLLVQLLRFLRADGDLTLLWAEWQGRRPEWELTDMVVWVTGASS

RN VKRRSLENGNLKEKDILVLPLDLADTSSHDI

RN ATKTVLQEFGRIDILVNNGGVAHASLVENTNMDIFKVLIEVNYLGTVSLTKCFLPHMMER

HP KQGKIVTVNSILGIISVPLSIGYCASKHALRGFFNGLRTELATYPGIIVSNICPGPVQSN
.*****...*

RN NQGKIVVMKS

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T84331) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10031> (SEQ ID Nos. 95, 105, and 115)

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Determination of the whole base sequence of the cDNA insert of clone HP10031 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 55-bp 5'-untranslated region, a 1464-bp ORF, and a 649-bp 3'-untranslated region. The ORF codes for a protein consisting of 487 amino acid residues and there existed eleven putative transmembrane domains. Figure 35 depicts the hydrophobicity/hydrophilicity profile, obtained

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by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight. When expressed in COS7 cells, an expression product of about 55 kDa was observed in the membrane fraction.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the was protein similar to the Caenorhabditis hypothetical CELK07H8 protein (GenBank Accession AF047659). Table 24 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein CELK07H8 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 44.2% in the entire region.

PCT/JP99/03929

93

Table 24

H	P MDGTETRQRRLDSCGKPGELGLPHPLSTGGLPVI
C	E MKGGGGIGDGKKDYQSAVHEGLTTFDQLGIALEDVGKSMDAETATPGGSLFSRVIFRFF
H	P EDGALRAPESQSVTPKPLETEPSRETAWSIGLQVTVPFMFAGLGLSWAGMLLDYFQHWP
	**
C	E ENSSLKSRTYDHSNDLVNMSVIPAESSYVLFFQVLFPFAVAGLGMVFAGLVLSIVVTW
HI	P FVEVKDLLTLVPPLVGLKGNLEMTLASRLSTAANTGQIDDPQEQHRVISSNLALIQVQ
	* * * * * * * * * * * * * * * * * *
CI	FEEIPEILILVPALLGLKGNLEMTLASRLSTLANLGHMDSSKQRKDVVIANLALVQVQ
H	VVGLLAAVAALLLGVVSREEVDVAKVELLCASSVLTAFLAAFALGVLMVCIVIGARKL
	**** * * * ** * * * **
CI	VVAFLASAFAAALAFIPSGDFDWAHGALMCASSLATACSASLVLSLLMVVVIVTSRKY
HI	NPDNIATPIAASLGDLITLSILALVSSFFYR-HKDSRYLTPLVCLSFAALTPVWVLIA
	**** ******* ** ** ** * * * * * * * * *
CE	NPDNVATPIAASLGDLTTLTVLAFFGSVFLKAHNTESWLNVIVIVLFLLLLPFWIKIAN
HI	SPPIVKILKFGWFPIILAMVISSFGGLILSKTVSKQQYKGMAIFTPVICGVGGNLVAI
CE	NEGTQETLYNGWTPVIMSMLISSAGGFILETAVRRYHSLSTYGPVLNGVGGNLAAV
HP	SRISTYLHMWSAPGVLPLQMKKFWPNPCSTFCTSEINSMSARVLLLLVVPGHLIF-
	.*.* *****
CE	SRLSTYFHKAGTVGVLPNEWTVSRF-TSVQRAFFSKEWDSRSARVLLLLVVPGHICFNF
HP	I-IYLVEGQSVINSQTFVVLYLLAGLIQVTILLYLAEVMVRLTWHQALDPDNHCIPY
	· · · · · · · · · · · · · · · · · · ·
CE	IQLFTLTSKNNVTPHGPLFTSLYMIAAIIQVVILLFVCQLLVALLWKWKIDPDNSVIPY
	TGLGDLLGTGLLALCFFTDWLLKSKAELGGISELASGPP
	*.******
CE	TALGDLLGTGLLFIVFLTTDHFDPKELTSS

Furthermore, the search of the GenBank using the base

sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

94

example, Accession No. AA334000) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10530> (SEQ ID Nos. 96, 106, and 116)

Determination of the whole base sequence of the CDNA insert of clone HP10530 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the consisting of a 80-bp 5'-untranslated region, a 1182-bp ORF, and a 95-bp 3'-untranslated region. The ORF codes for a protein consisting of 393 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 36 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 46 kDa that was somewhat larger than the molecular weight of 44,912 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 45.5 kDa from which the secretory signal is considered to have been cleaved. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine at position 23. When expressed in COS7 cells, an expression product of about 43 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana hypothetical protein IG002N01 (GenBank Accession No. AF007269). Table 25 shows the comparison between amino acid sequences of the

PCT/JP99/03929

95

human protein of the present invention (HP) and the A. thaliana hypothetical protein IG002N01 (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 27.0% in the N-terminal region of 355 amino acid residues.

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PCT/JP99/03929

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Table 25

	HP	MRTLFNLLWL
5	AT	. MELTSFQKSPSSNDVVSFSVSLVRNSMARRRRSSAAESLKRRNDGYESLCQVVQQDSDRR
	HP	ALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVVTDLKAESVVLEHRSYCSA
		·····*·* ** ** · · · · · ** · · · · · ·
	ΑT	LITIFVIFFIVIPAVSIAVYKVKFADRVIQTESSIRQKGIVKTDINFQEILTEHSKAS
	HP	KARDRHFAGDVLGYVTPWNSHGYDVTKVFGSKFTQISPVWLQ-LKRRGREMFEVTGLHDV
10		******* ***** *** *** *** *** *********
	AT	ENSTRHYDYPVLAYITPCQGSGLVLEGR-HNADKGWIQELRSRGNALSASKGLPKL
	HP	DQGWMRAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDGF
		* * . ***. *
	AT	YNSCIFHALKRMNFFTLELVNFNTYLVIMFALNS-REMEYNGIVLESWSRWAAYGVL
15	HP	${\tt VVEVWNQLLSQKRVGLIHMLTHLAEALHQARLLALLVIPPAITPGTDQLGMFTHKEFEQL}$
		* . * * . * . * .
	AT	${\tt HDPDLRKMALKFVKQLGDALHSTSSPRNNQQHMQFMYVVGPPRSEKLQMYDFGPEDLQFL}$
	HP	APVLDGFSLMTYDYSTAHQPGPNAPLSWVRACVQ-VLDPKSKWRSKILLGLNFYGM

20	AT	${\tt KDSVDGFSLMTYDFSNPQNPGPNAPVKWIDLTLKLLLGSSNNIDSNIARKVLLGINFYGN}$
	HP	DYATSKDAREPVVGARYIQTLKDHRPRMVWDSQASEHFFEYKKSRSGRHVVFYPTLKSLQ
		** * * . * . * . * . * * . * . * . * . * . * * . *
	ΑT	DFVISGGGGGAITGRDYLALLQKHKPTFRWDKESGEHLFMYRDDKNIKHAVFYPTLMSIL
	HP	VRLELARELGVGVSIWELGQGLDYFYDLL
25		. ** * * * * * * * * * * * * * * * * *
	AT	LRLENARLWGIGISIWEIGQDKGHFGKYAEASLEASSIFSGHTFDMQFRTNPRQLSRNGS

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA302913) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the

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PCT/JP99/03929

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protein of the present invention.

<HP10541> (SEQ ID Nos. 97, 107, and 117)

Determination of the whole base sequence of the cDNA insert of clone HP10541 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 7-bp 5'-untranslated region, a 591-bp ORF, and a 113-bp 3'untranslated region. The ORF codes for a protein consisting of 196 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 37 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of 23 kDa that was somewhat larger than the molecular weight of 21,553 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 20 kDa from which the secretory signal is considered to have been cleaved and a product of 23 kDa which is considered to have a sugar chain being attached. Application of the (-3,-1)rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glycine at position 41. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Leu-Thr at position 185).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human zymogen membrane protein (GenBank Accession No. AF056492). Table 26 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human zymogen membrane protein (ZM). Therein, the marks of -, *, and . represent a

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PCT/JP99/03929

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gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.6% in the C-terminal region of 133 amino acid residues.

Table 26

HP MWRVPGTTRRPVTGESPGMHRPEAMLLLLTLALLGGPTWAGKMYGPGGGKYFS-TTEDYD 10 **.*** ** . . . * ZM MLTVALLALLCASASGNAIQARSSSYSGEYGSGGGKRFSHSGNQLD HP HEITGLRVSVGLLLVKSVQVKLGDSWDVKLGALGGNTQEVTLQPGEYITKVFVAFQAFLR ZM GPITALRVRVNTYYIVGLQVRYGKVWSDYVGGRNGDLEEIFLHPGESVIQVSGKYKWYLK 15 HP GMVMYTSKDRYFYFGKLDGQISSAYPSQEGQVLVGIYGQYQLLGIKSIGFEWN-YPLEEP .* * . . ** * *. * *..**..*. ** ZM KLVFVTDKGRYLSFGKDSGTSFNAVPLHPNTVLRFISGRSGSL-IDAIGLHWDVYPTSCS HP TTEPPVNLTYSANSPVGR 20 ZM RC

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA340605) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10550> (SEQ ID Nos. 98, 108, and 118)

Determination of the whole base sequence of the cDNA

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insert of clone HP10550 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 241-bp 5'-untranslated region, a 324-bp ORF, and a 86-bp 3'-untranslated region. The ORF codes for a protein consisting of 107 amino acid residues and there existed one putative transmembrane domain. Figure 38 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA348310) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10590> (SEQ ID Nos. 99, 109, and 119)

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Determination of the whole base sequence of the cDNA insert of clone HP10590 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 77-bp 5'-untranslated region, a 1053-bp ORF, and a 180-bp 3'-untranslated region. The ORF codes for a protein consisting of 350 amino acid residues and there existed one putative transmembrane domain. Figure 39 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 40 kDa that was almost identical with the molecular weight of 39,285 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of

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43 kDa which is considered to have a sugar chain being attached. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Asn-Ser at position 144 and Asn-Leu-Thr at position 328).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA461346) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10591> (SEQ ID Nos. 100, 110, and 120)

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Determination of the whole base sequence of the cDNA insert of clone HP10591 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 232-bp 5'-untranslated region, a 324-bp ORF, and a 844-bp 3'-untranslated region. The ORF codes for a protein consisting of 107 amino acid residues and there existed one putative transmembrane domain. Figure 40 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,328 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H09424) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein

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PCT/JP99/03929

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of the present invention.

<HP01462> (SEQ ID Nos. 121, 131, and 141)

Determination of the whole base sequence of the CDNA insert of clone HP01462 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 121-bp 5'-untranslated region, a 1452-bp ORF, and a 477-bp 3'-untranslated region. The ORF codes for a protein consisting of 483 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 41 depicts the hydrophobicity/hydrophilicity profile, by the Kyte-Doolittle method, of the present obtained protein. In vitro translation resulted in formation of a translation product of 72 kDa that was larger than the molecular weight of 55,838 predicted from the Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine position 21.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein similar the was to Caenorhabditis hypothetical protein ZK1058.4 (EMBL Accession No. 235604). Table 27 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein ZK1058.4 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.6% in the entire region.

102

Table 27

	HP	${\tt MKAFHTFCVVLLVFGSVSEAKFDDFEDEEDIVEYDDNDFAEFEDVMEDSVTESPQRVIIT}$
		* *
5	CE	MKIVWIFLIFFIGFAIST
	HP	EDDE-DETTVELEGQDENQEGDFEDADTQEGDTESEPYDDEEFEGYEDKPD
		.*.* .* . *. *
	CE	DDNEFAEFEDEFVGSSATQAPEIQREGEPPVLKQKDDFEEEDFGVVEEEPEEAEKVREAD
	HP	TSSSKNKDPITIVDVPAHLQNSWESYYLEILMVTGLLAYIMNYIIGKNKNSRLAQAWFNT
10		***** .* .* .* ** **.***.* .* *.
,	CE	${\tt SDDAAPAQPLKFADVPAHFRSNWASYQVEGIVVLIILIYMTNYLIGKTTNASIAQTIFDM}$
	HP	HRELLESNFTLVGDDGTNKEATSTGKLNQENEHIYNLWCSGRVCCEGMLIQLRFLKRQDL
		* ***.***** ** **.***
	CE	${\tt CRPTLEEQFAVVGDDGTTDLDKMIPSLKHDTDSTFSAWCTGRVNVNSLFLQMKMVKRQDV}$
15	HP	$\verb LNVLARMMRPVSDQVQIKVTMN-DEDMDTYVFAVGTRKALVRLQKEMQDLSEFCSDKPKS $
		*. * .* ** * * **** * . *** ** *
	CE	${\tt VSRIMEMFTPSGDKMTIKASLETTNDTDPLIFAVGEKKIASKYFKEMLDLNSFASERKQA}$
	HP	${\tt GAKYGLPDSLAILSEMGEVTDGMMDTKMVHFLTHYADKIESVHFSDQFSGPKIMQEEGQP}$
		.** .* .* .* .*.****.
20	CE	${\tt AQQFNLPASWQVYADQNEVVFSILDPGVVSLLKKHEDAIEFIHISDQFTGPKPAEGESYT}$
	HP	${\tt LKLPDTKRTLLFTFNVPGSGNTYPKDMEALLPLMNMVIYSIDKAKKFRLNREGKQKADKN}$
		.*** *
	CE	$-\mathtt{RLPEAQRYMFVSLNLQYLGQDEESVMEILNLVFYLIDKARKMKLSKDAKVKAERR}$
	HP	${\tt RARVEENFLKLTHVQRQEAAQSRREEKKRAEKERIMNEEDPEKQRRLEEAALRREQKKLE}$
25		मं मं क्षेत्रक प्रेष्ठ प्रेष्ठ प्रेष्ठे प्रे प्रेष्ठे प्रेष्ठे प्रेष्ठे प्रेष्ठे प्रेष्ठे प्रेष्ठे प्रेष्ठे प्र
	CE	RKEFEDAFLKQTHQFRQEAAQARREEKTRERKQKLMDESDPERQKRLEAKELKREAKA
	HP	KKQMKMKQIKVKAM
٠		* *****
	CE	-KSPKMKQLKVK
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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

103

example, Accession No. AA307793) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP02485> (SEQ ID Nos. 122, 132, and 142)

Determination of the whole base sequence of the cDNA insert of clone HP02485 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 69-bp 5'-untranslated region, a 1005-bp ORF, and a 1672-bp 3'untranslated region. The ORF codes for a protein consisting of 334 amino acid residues and there existed one putative transmembrane domain. Figure 42 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 36 kDa that was almost identical with the molecular weight of 38,171 predicted from the ORF. When expressed in COS7 cells, an expression product of about 23 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis elegans hypothetical protein W01A11.2 (GenBank Accession No. U64852). Table 28 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein W01A11.2 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 45.5% in the entire region.

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PCT/JP99/03929

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Table 28

HP MVEFAPLFMPWERRLQTLAVLQFVFSFLALAEICT-V 5 CE MRLRLSSISGKAKLPDKEICSSVSRILAPLLVPWKRRLETLAVMGFIFMWVILPIMDLWV HP GFIALLFTRFWLLTVLYAAWWYLDRDKPRQGGRHIQAIRCWTIWKYMKDYFPISLVKTAE CE PFHVLFNTRWWFLVPLYAVWFYYDFDTPKKASRRWNWARRHVAWKYFASYFPLRLIKTAD 10 HP LDPSRNYIAGFHPHGVLAVGAFANLCTESTGFSSIFPGIRPHLMMLTLWFRAPFFRDYIM * ..*** * ****...**...*...*...*...*.. CE LPADRNYIIGSHPHGMFSVGGFTAMSTNATGFEDKFPGIKSHIMTLNGQFYFPFRREFGI HP SAGLVTSEKESAAHILNRKGGGNLLGIIVGGAQEALDARPGSFTLLLRNRKGFVRLALTH * .. .*** ...* * *. .*. *** *** **. * * * * **. ** . ** 15 CE MLGGIEVSKESLEYTLTKCGKGRACAIVIGGASEALEAHPNKNTLTLINRRGFCKYALKF HP GAPLVPIFSFGENDLFDQIPNSSGSWLRYIQNRLQKIMGISLPLFHGRGVF-QYSFGLIP CE GADLVPMYNFGENDLYEQYENPKGSRLREVQEKIKDMFGLCPPLLRGRSLFNQYLIGLLP HP YRRPITTVVGKPIEVQKTLHPSEEEVNQLHQRYIKELCNLFEAHKLKFNIPADQHLEFC 20 **,*.*.**.***.** * .* .*...**..* ..*.**..* CE FRKPVTTVMGRPIRVTQTDEPTVEQIDELHAKYCDALYNLFEEYKHLHSIPPDTHLIFO

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D25664) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02798> (SEQ ID Nos. 123, 133, and 143)

Determination of the whole base sequence of the cDNA

105

insert of clone HP02798 obtained from cDNA library of human line HT-1080 revealed the structure fibrosarcoma cell consisting of a 31-bp 5'-untranslated region, a 804-bp ORF. and a 301-bp 3'-untranslated region. The ORF codes for a protein consisting of 267 amino acid residues and there existed four putative transmembrane domains. Figure depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 29 kDa that was almost identical with the molecular weight of 30,778 predicted from the ORF. When expressed in COS7 cells, an expression product of about 26 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human DHHC-containing cysteinerich protein (GenBank Accession No. U90653). Table 29 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human DHHCcontaining cysteine-rich protein (DH). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.0% in the intermediate region of 100 amino acid residues. The positions of seven cysteines were conserved between the two proteins. The protein of the present invention also had the DHHC (Asp-His-His-Cys) sequence.

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PCT/JP99/03929

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Table 29

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D79050) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

25 <HP10041> (SEQ ID Nos. 124, 134, and 144)

Determination of the whole base sequence of the cDNA insert of clone HP10041 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 12-bp 5'-untranslated region, a 321-bp ORF, and a 286-bp 3'-untranslated region. The ORF codes for a protein consisting of 106 amino acid residues and there existed one putative transmembrane domain. Figure 44 depicts

PCT/4P99 45929

107

the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 12,060 predicted from the ORF. When expressed in COS7 cells, an expression product of about 13 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis hypothetical protein K10B2.4 (GenBank Accession No. U28730). Table 30 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein K10B2.4 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 62.1% in the entire region.

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Table 30

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Furthermore, the search of the GenBank using the base

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sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H20098) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10246> (SEQ ID Nos. 125, 135, and 145)

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Determination of the whole base sequence of the cDNA insert of clone HP10246 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 110-bp 5'-untranslated region, a 675-bp ORF, and a 79-bp 3'-untranslated region. The ORF codes for a protein consisting of 224 amino acid residues and there existed five putative transmembrane domains. Figure 45 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 23 kDa that was somewhat smaller than the molecular weight of 25,244 predicted from the ORF. When expressed in COS7 cells, an expression product of about 21 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human putative transmembrane domain protein (GenBank Accession No. Y18007). Table 31 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human putative seven transmembrane domain protein (TM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that

PCT/JP99/03929

109

of the protein of the present invention, respectively. The both proteins shared a homology of 93.3% in the entire region.

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Table 31

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA453931) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10392> (SEQ ID Nos. 126, 136, and 146)

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Determination of the whole base sequence of the cDNA insert of clone HP10392 obtained from cDNA library of human osteosarcoma cell line U-2 OS revealed the structure

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PCT/JP99/03929

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consisting of a 24-bp 5'-untranslated region, a 777-bp ORF, and a 726-bp 3'-untranslated region. The ORF codes for a protein consisting of 258 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 46 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 34 kDa that was somewhat larger than the molecular weight of 29,623 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 49.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H15999) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention. In addition, partial identity with the hypothetical protein KIAA0384 (Accession No. AB002382) was observed, although the hypothetical protein had a different ORF.

25 <HP10489> (SEQ ID Nos. 127, 137, and 147)

Determination of the whole base sequence of the cDNA insert of clone HP10489 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 137-bp 5'-untranslated region, a 333-bp ORF, and a 189-bp 3'-untranslated region. The ORF codes for a protein consisting of 110 amino acid residues and there existed two putative transmembrane domains. Figure 47 depicts the

111

hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 19 kDa that was somewhat larger than the molecular weight of 12,010 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA262162) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10519> (SEQ ID Nos. 128, 138, and 148)

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Determination of the whole base sequence of the cDNA insert of clone HP10519 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 67-bp 5'-untranslated region, a 276-bp ORF, and a 367-bp 3'untranslated region. The ORF codes for a protein consisting of 91 amino acid residues and there existed one putative transmembrane domain. Figure 48 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method. of the present protein. translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 10,275 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W16639) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein

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PCT/JP99/03929

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of the present invention.

<HP10531> (SEQ ID Nos. 129, 139, and 149)

Determination of the whole base sequence of the cDNA insert of clone HP10531 obtained from cDNA library of human 5 osteosarcoma cell line Saos-2 revealed the consisting of a 55-bp 5'-untranslated region, a 1035-bp ORF, and a 1092-bp 3'-untranslated region. The ORF codes for a protein consisting of 344 amino acid residues and there 10 existed five putative transmembrane domains. Figure 49 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R50695) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10574> (SEQ ID Nos. 130, 140, and 150)

Determination of the whole base sequence of the cDNA insert of clone HP10574 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 210-bp 5'-untranslated region, a 1287-bp ORF, and a 1276-bp 3'-untranslated region. The ORF codes for a protein consisting of 428 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the intermediate region. Figure 50 depicts the hydrophobicity/hydrophilicity profile, obtained

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PCT/JP99/03929

113

by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 36.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Drosophila melanogaster GOLIATH protein (SWISS-PROT Accession No. Q06003). Table 32 shows the comparison between amino acid sequences of the human of the present invention (HP) and the melanogaster GOLIATH protein (DM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The intermediate region of 169 amino acids of the protein of the present invention shared a homology of 41.4% with the N-terminal region of the D. melanogaster GOLIATH protein.

PCT/JP99/03929

114

Table 32

HP MGPPPGAGVSCRGGCGFSRLLAWCFLLALSPQAPGSRGAEAVWTAYLNVSWRVPHTGVNR HP TVWELSEEGVYGQDSPLEPVAGVLVPPDGPGALNACNPHTNFTVPTVWGSTVQVSWLALI HP QRGGGCTFADKIHLAYERGASGAVIFNFPGTRNEVIPMSHPGAVDIVAIMIGNLKGTKIL 5 DM MQLEKMQIKGKTRNIAAVITYQNIGQDLS HP QSIQRGIQVTMVIEVGKK---HGPWVNHYSIFFVSVSFFIITAATVGYFIFYSARRLRNA . .*. *..*** **.*** .*.* * .**. * *... DM LTLDKGYNVTISIIEGRRGVRTISSLNRTSVLFVSIS-FIV-DDILCWLIFYYIQRFRYM 10 HP RAQSRKQRQLKADAKKAIGRLQLRTLKQGDKEIGPDGDSCAVCIELYKPNDLVRILTCNH DM QAKDQQSRNLCSVTKKAIMKIPTKTGKFSD-EKDLDSDCCAICIEAYKPTDTIRILPCKH HP IFHKTCVDPWLLEHRTCPMCKCDILKALGIEVDVEDGSVSLQVPVSNEISNSASSHEEDN 15 ***.*.******** * * * * DM EFHKNCIDPWLIEHRTCPMCKLDVLKFYGYVVGDQIYQTPSPQHTAPIASIEEVPVIVVA HP RSETASSGYASVQGTDEPPLEEHVQSTNESLQLVNHEANSVAVDVIPHVDNPTFEEDETP DM VPHGPQPLQASNMSSFAPSHYFQSSRSPSSSVQQQLAPLTYQPHPQQAASERGRRNS 20 HP NQETAVREIKS DM APATMPHAITASHQVTDV

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA155685) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

115

The present invention provides human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors for these DNAs as well as eucaryotic cells expressing these DNAs. All of the proteins of the present invention are secreted or exist in the cell membrane. so that they are considered to be proteins controlling the proliferation and/or the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents which act to control the proliferation and/or differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for large-scale expression of these proteins. Cells into which these genes are introduced to express these proteins, can be utilized for detection of the corresponding receptors and ligands, screening of novel lowmolecular pharmaceuticals, and so on.

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The present invention also provides genes corresponding to polynucleotide sequences disclosed "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which CDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed Such methods include the preparation of probes or herein.

116

primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

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Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; which are incorporated by reference Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 Bl, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide disclosed sequences herein have partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished

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through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153: 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more

118

preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

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disclosed polynucleotides Species homologs of the and proteins are also provided by the present invention. As herein, "species homologue" a is а protein polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides

PCT/JP99/03929

119

capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table 33 below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

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Table 33

	,		
Polynucleotide	Hybrid		Wash
Hybrid	_	and Buffer [†]	Temperature
	(bp) [‡]		and Buffer†
DNA : DNA	≥50	1	65°C; 0.3×SSC
		42°C; 1×SSC,50% formamide	
DNA : DNA	< 50	T _B *; 1×SSC	T _B *; 1×SSC
DNA: RNA	≥50	67°C; 1×SSC -or-	67°C; 0.3×SSC
li.		45℃; 1×SSC,50% formamide	
DNA: RNA	<50	T _D *; 1×SSC	T _D *; 1×SSC
RNA: RNA	≥50	70°C; 1×SSC -or-	70°C; 0.3×SSC
•		50°C; 1×SSC,50% formamide	
RNA: RNA	<50	T _F *; 1×SSC	T _F *; 1×SSC
DNA : DNA	≥50	65°C; 4×SSC -or-	65°C; 1×SSC
		42°C; 4×SSC,50% formamide	
DNA : DNA	<50	T _H *; 4×SSC	T _H *; 4×SSC
DNA: RNA	≥50	67°C; 4×SSC -or-	67°C; 1×SSC
		45°C; 4×SSC,50% formamide	
DNA: RNA	< 50	T _J *; 4×SSC	T _J *; 4×SSC
RNA: RNA	≥50	70°C; 4×SSC -or-	67°C; 1×SSC
		50°C; 4×SSC,50% formamide	
RNA: RNA	<50	T _L *; 2×SSC	T _L *; 2×SSC
DNA : DNA	≥50	50°C; 4×SSC -or-	50°C; 2×SSC
		40°C; 6×SSC,50% formamide	
DNA : DNA	<50	T _N *; 6×SSC	T _N *; 6×SSC
DNA : RNA	≥50	55°C; 4×SSC -or-	55°C; 2×SSC
		42°C; 6×SSC,50% formamide	
DNA: RNA	<50		T _P *; 6×SSC
RNA: RNA	≥50		60°C; 2×SSC
•		45°C; 6×SSC,50% formamide	
RNA: RNA	<50		T _R *; 4×SSC
	DNA: DNA DNA: RNA DNA: RNA DNA: RNA RNA: RNA RNA: RNA DNA: DNA DNA: DNA DNA: RNA DNA: RNA DNA: RNA DNA: RNA DNA: RNA RNA: RNA DNA: RNA RNA: RNA DNA: RNA DNA: RNA DNA: RNA DNA: RNA DNA: RNA	Hybrid Length (bp)‡ DNA : DNA ≥50 DNA : DNA ≥50 DNA : RNA ≥50 DNA : RNA ≥50 RNA : RNA ≥50 RNA : RNA ≥50 DNA : DNA ≥50 DNA : RNA ≥50 DNA : RNA ≥50 RNA : RNA ≥50 RNA : RNA ≥50 DNA : DNA ≥50 DNA : DNA ≥50 DNA : RNA ≥50 RNA : RNA ≥50	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

 \dagger : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than

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121

50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m (°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m (°C)=81.5 + 16.6(log₁₀[Na*]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na*] is the concentration of sodium ions in the hybridization buffer ([Na*] for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

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PCT/JP99/03929

122

CLAIMS

- 1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID Nos. 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.
- 2. An isolated DNA coding for the protein according to Claim 1.
- 3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140.
- 4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID Nos. 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150.
- 5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eucaryotic cells.
- 6. A transformed eucaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 2 and of producing the protein according to Claim 1.



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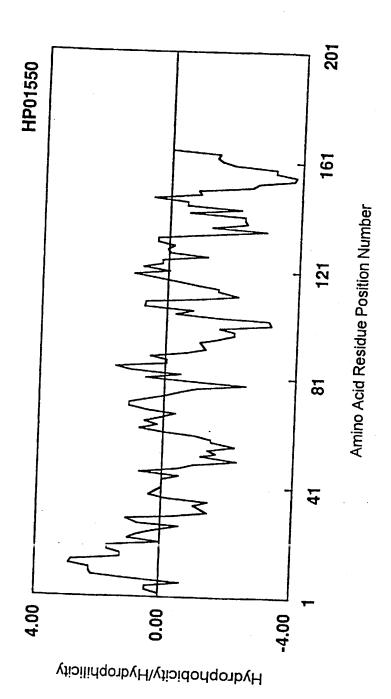


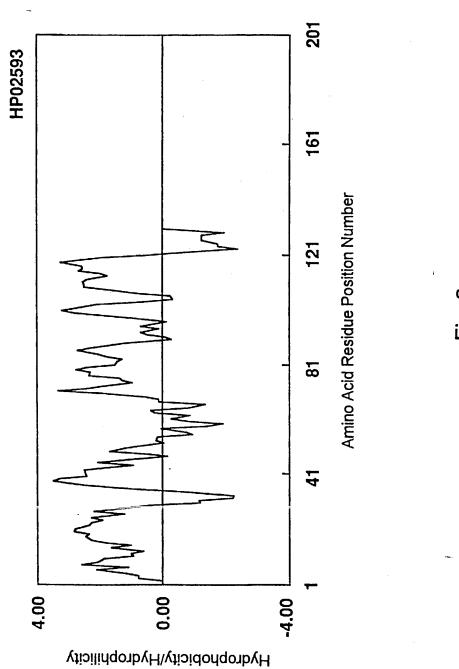
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(72) Inventors; and (75) Inventors/Applicants (for US only); KATO, Seishi [JF 3-46-50, Wakamatsu, Sagabahara-shi, Kana 229-0014 (JP) KIMURA, Tomoko [JP/JP]; 302, 4-Nishiikuta, Tama ku, Kawasaki-shi, Kanagawa 214-(JP).	gawa Before the expiration of the time limit for amending the claims			
	(88) Date of publication of the international search report: 4 May 2000 (04.05.00)			

(54) Title: HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAS ENCODING THESE PROTEINS

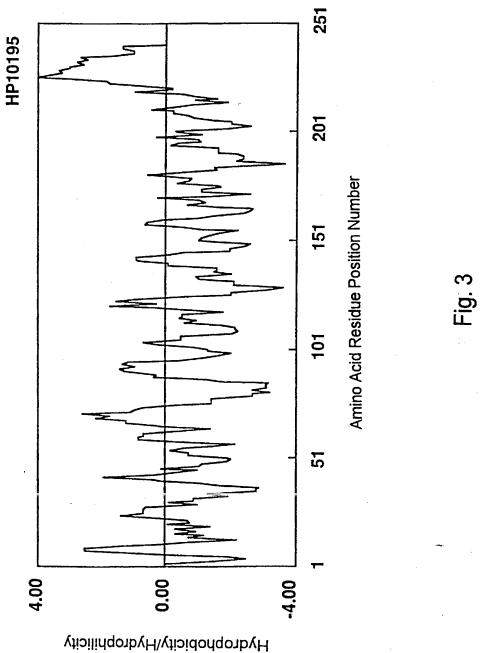
(57) Abstract

The present invention provides human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors for these DNAs as well as eucaryotic cells expressing these DNAs.



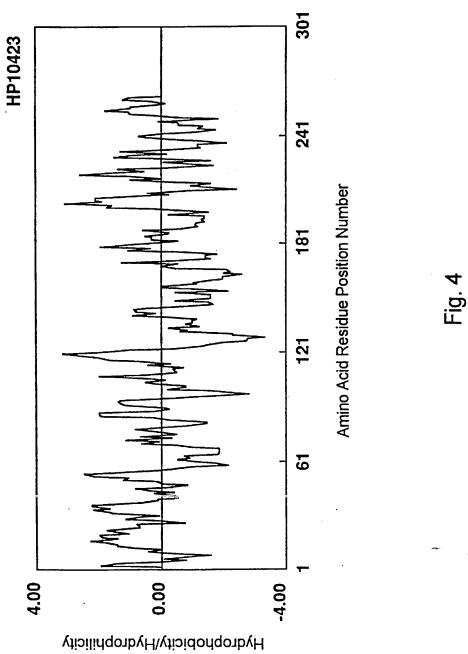


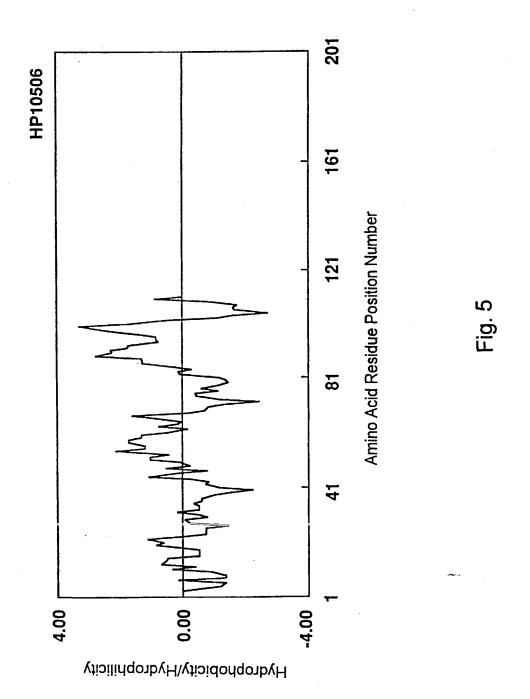
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PCT/JP99/03929

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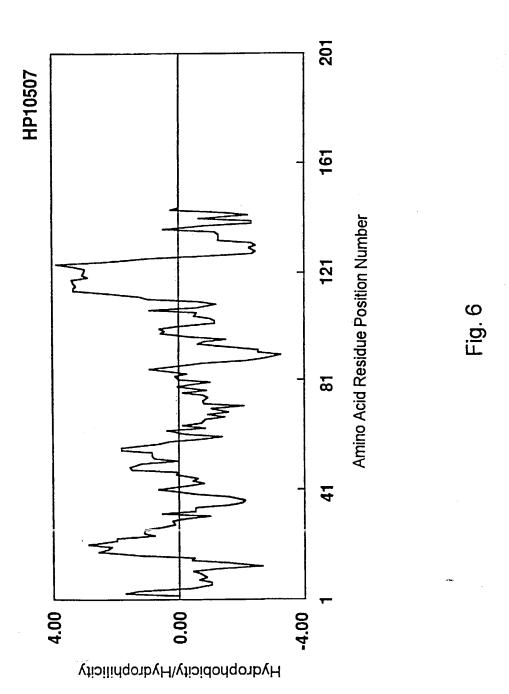


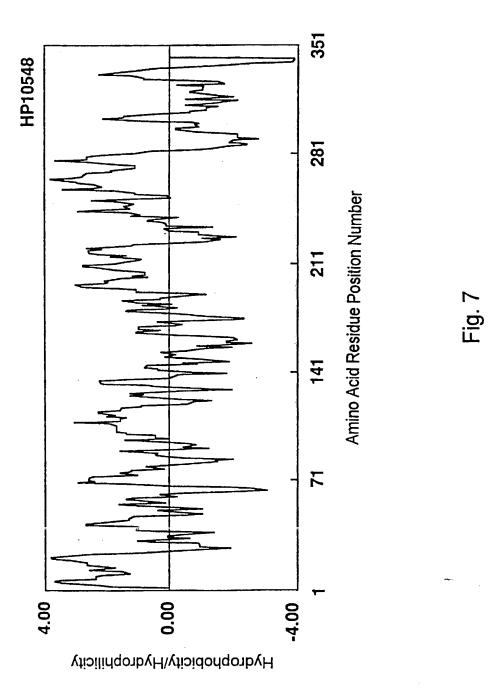


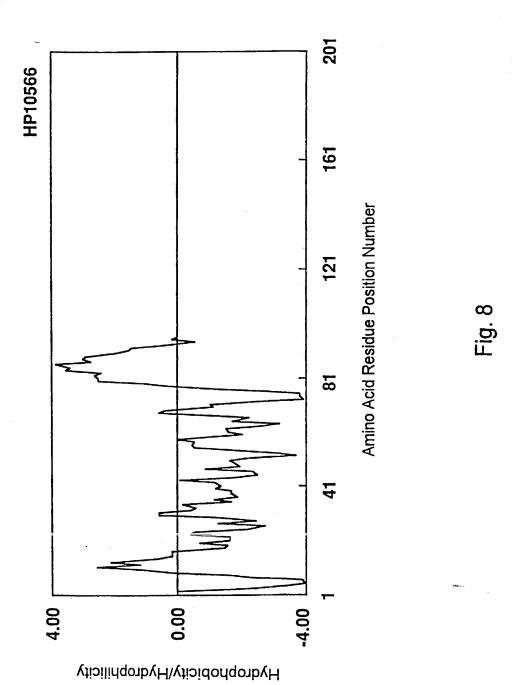
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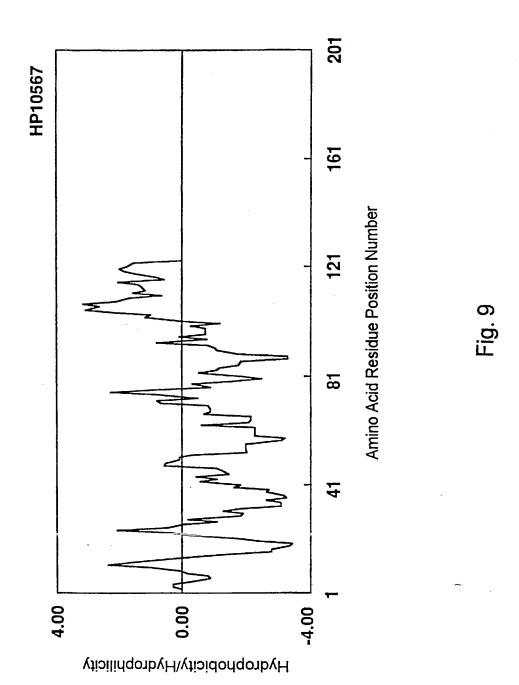
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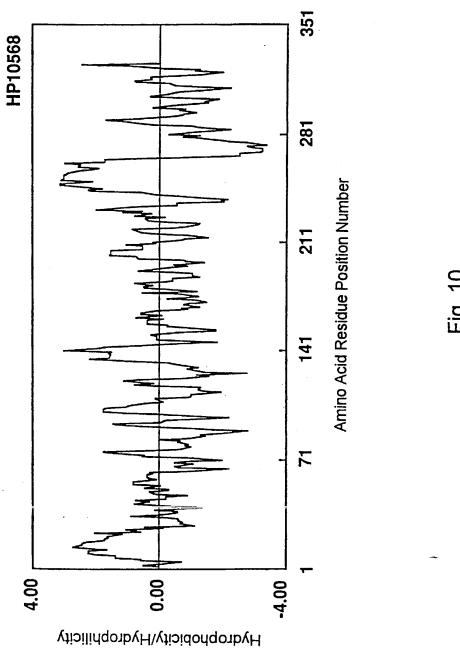
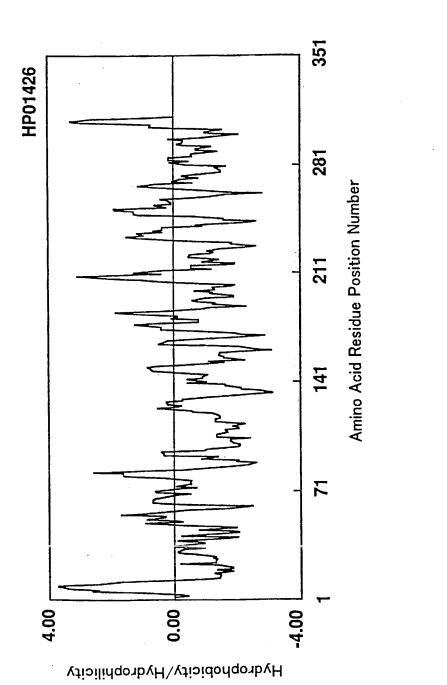


Fig. 10



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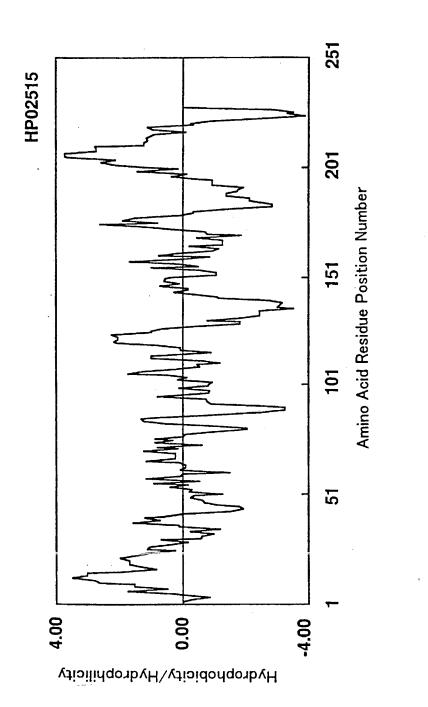
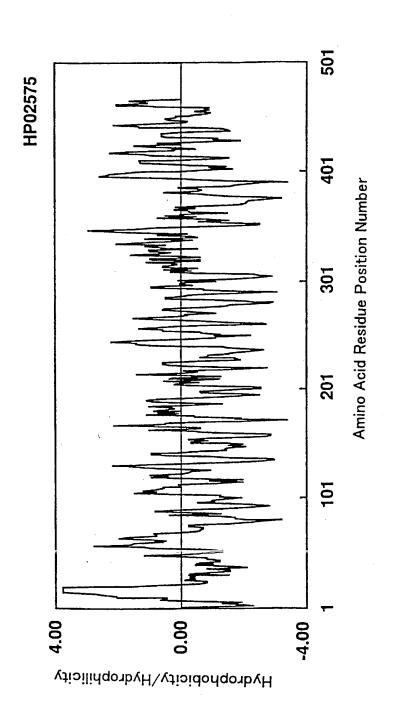
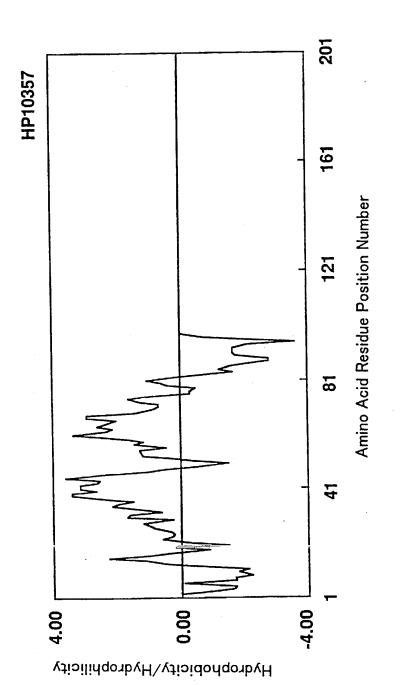


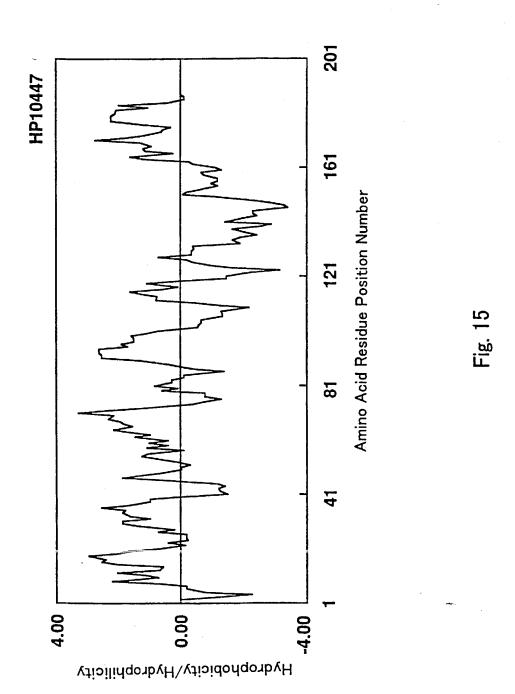
FIG. 12

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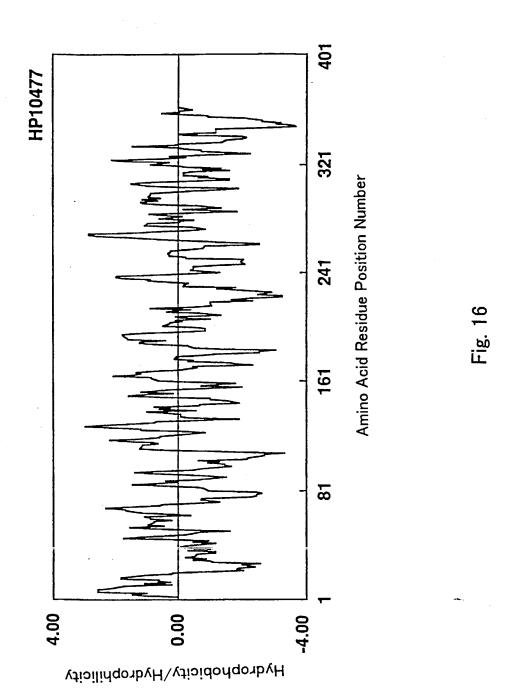
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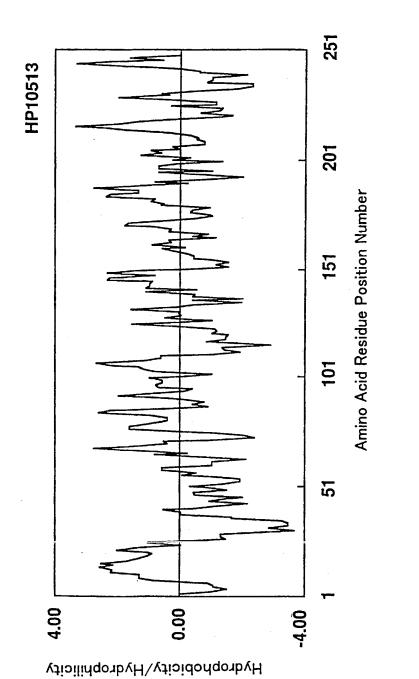






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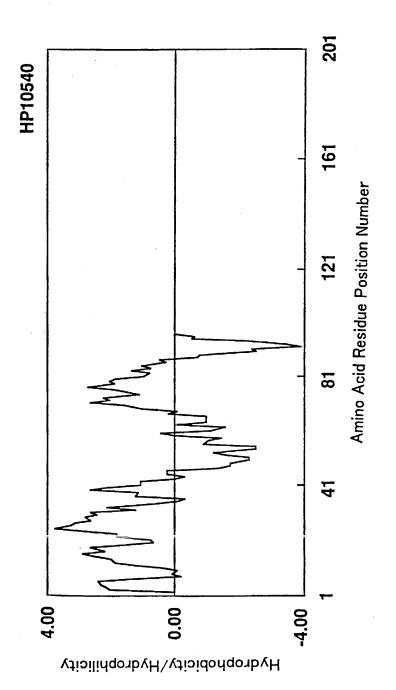
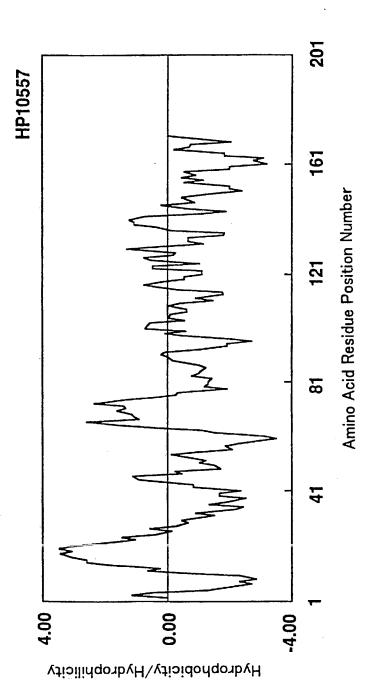
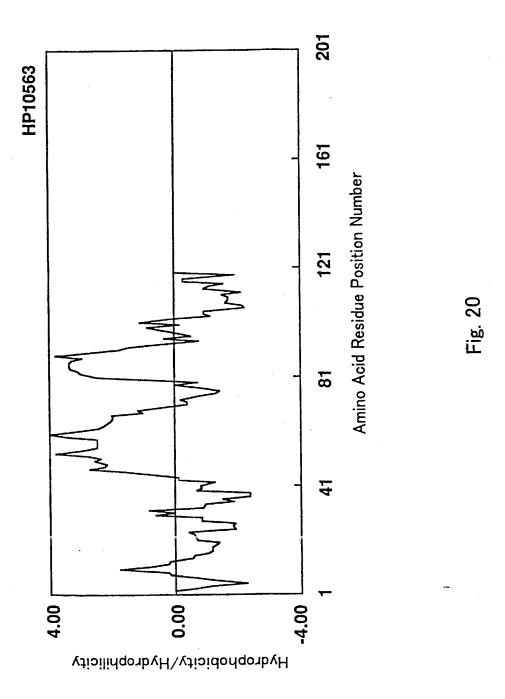


Fig. 18





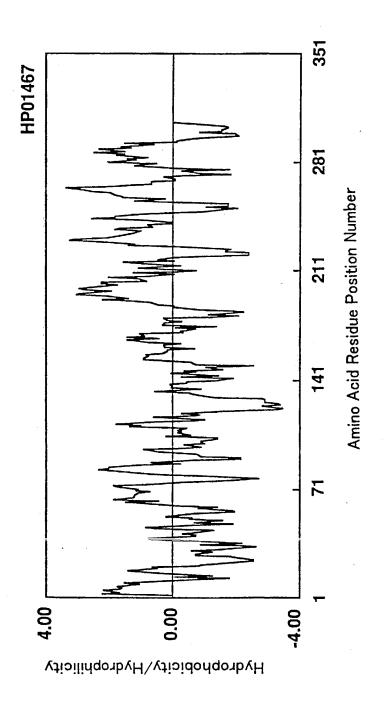


Fig. ZI

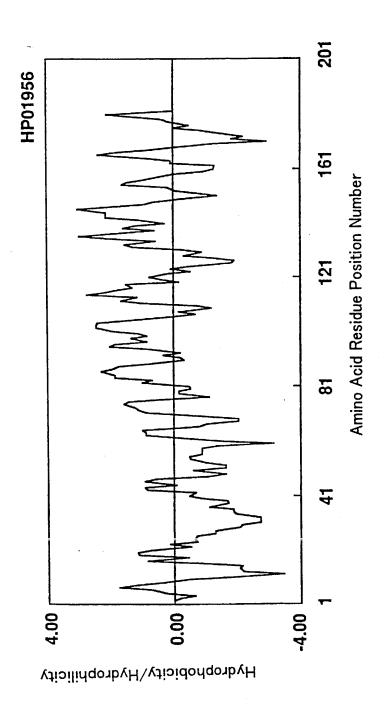


Fig.22

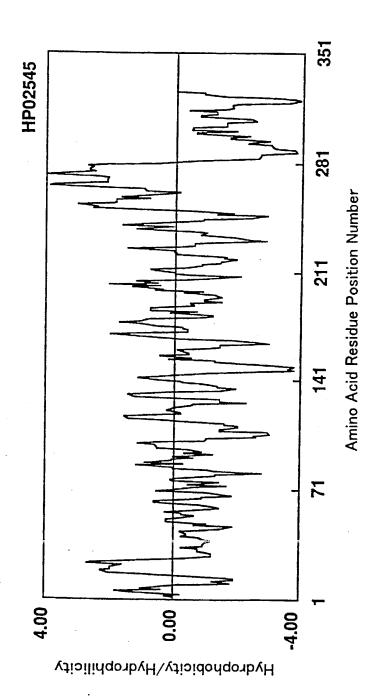


Fig. 23

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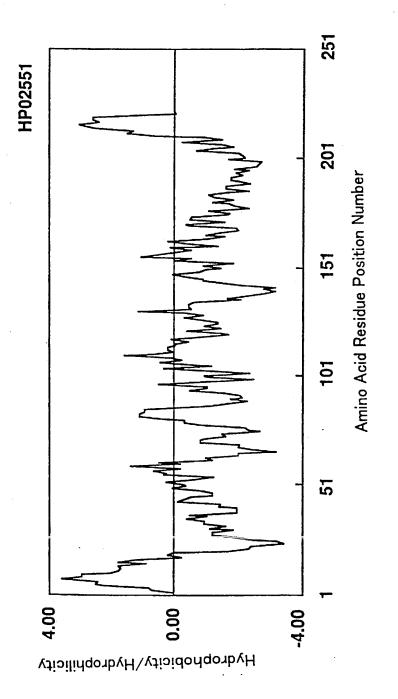
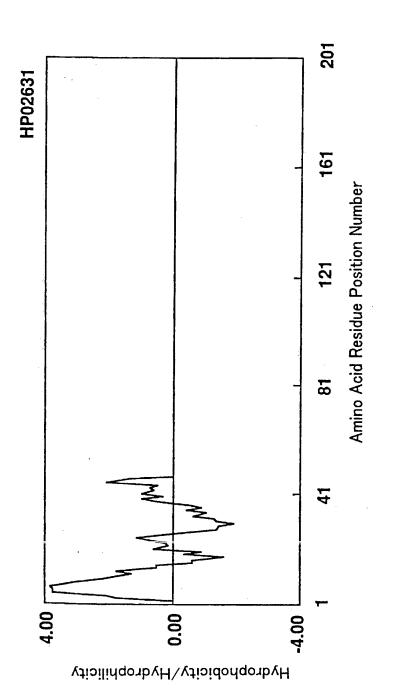


FIg. 24



Ig. 25

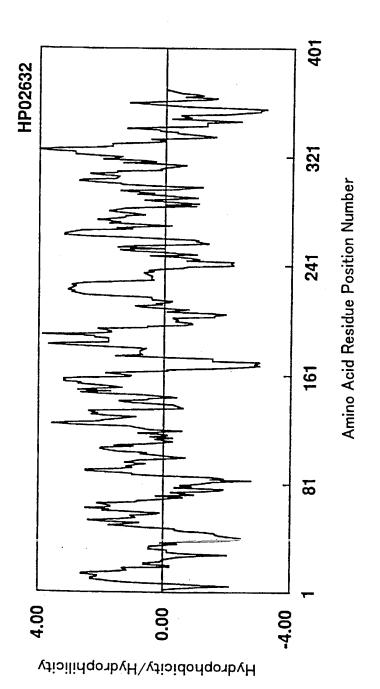


Fig. 26

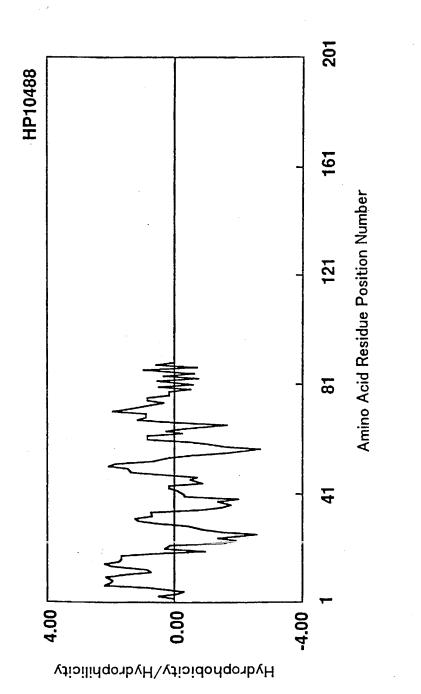


Fig.27

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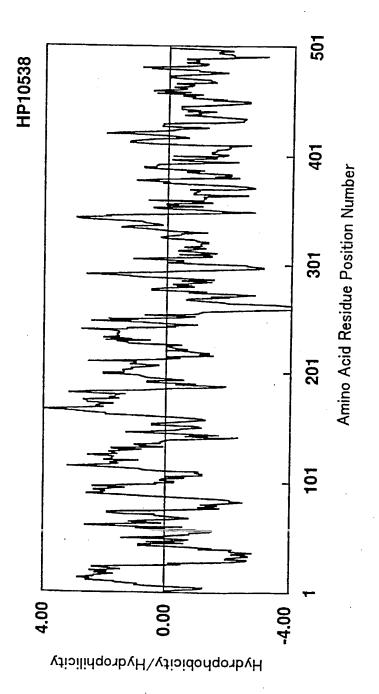


Fig. 28

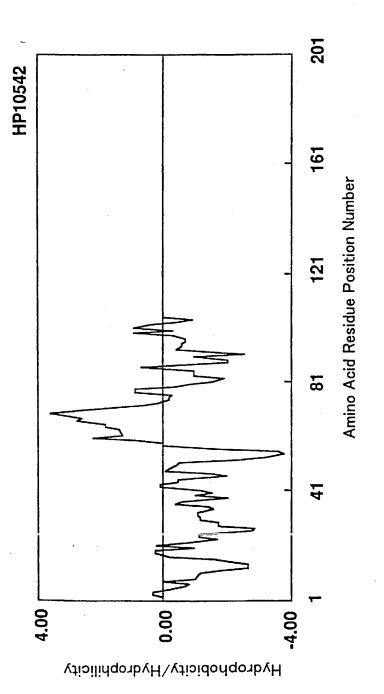


Fig. 29

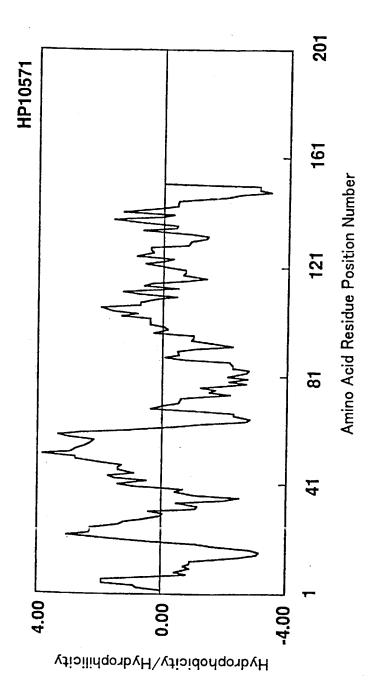


Fig. 30

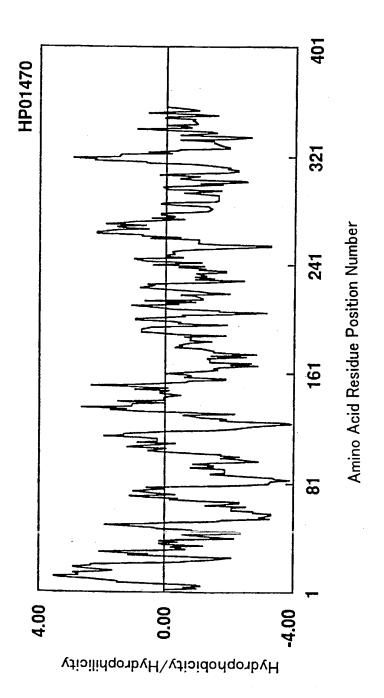


Fig. 31

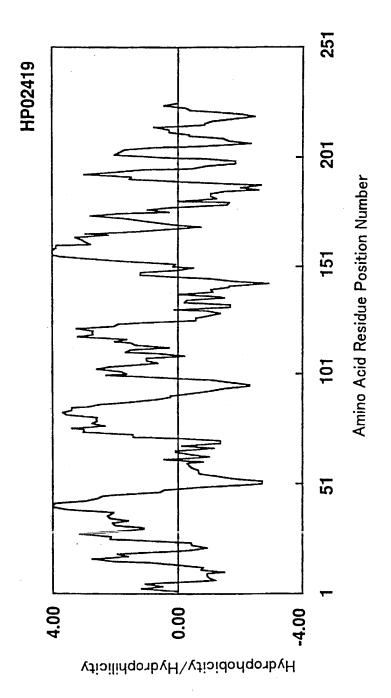
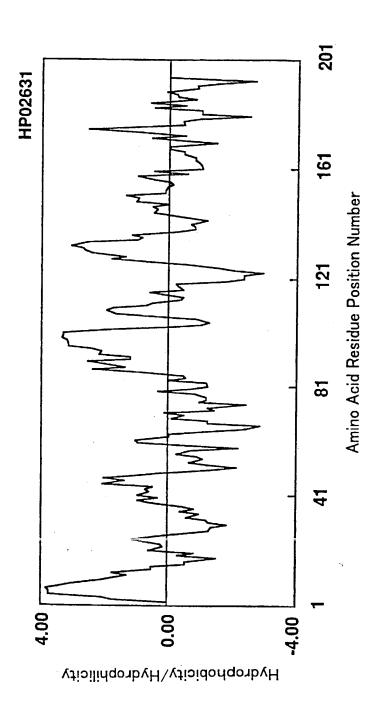


Fig.32

WO 00/05367

PCT/JP99/03929



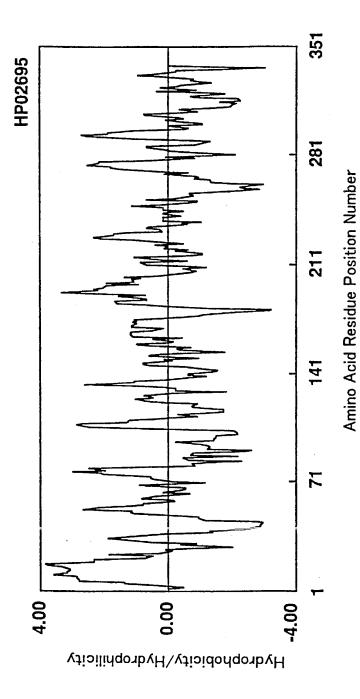


Fig. 34

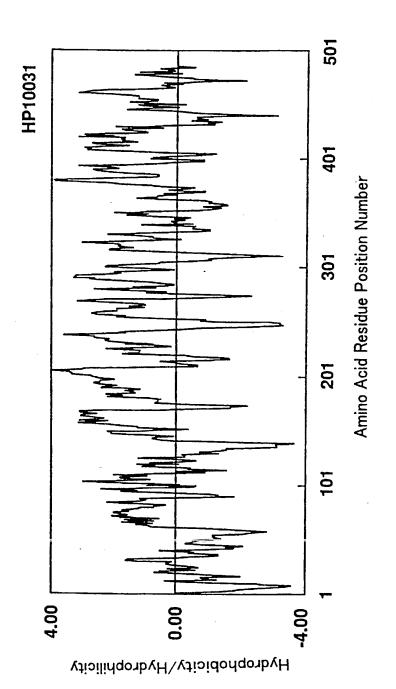


Fig. 35

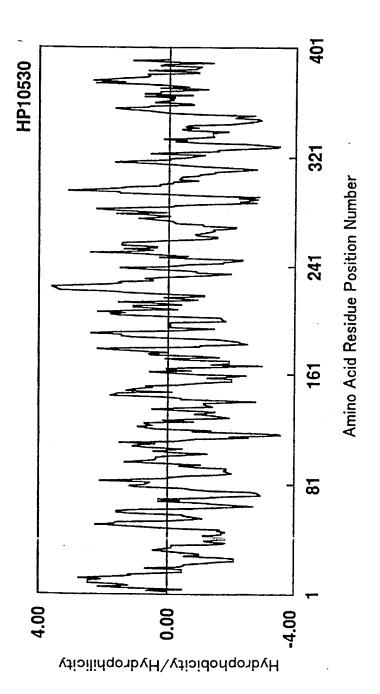
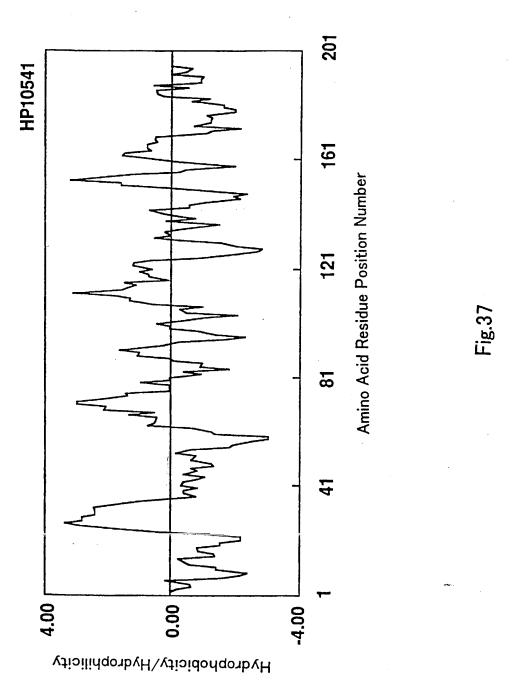


Fig. 36

WO 00/05367



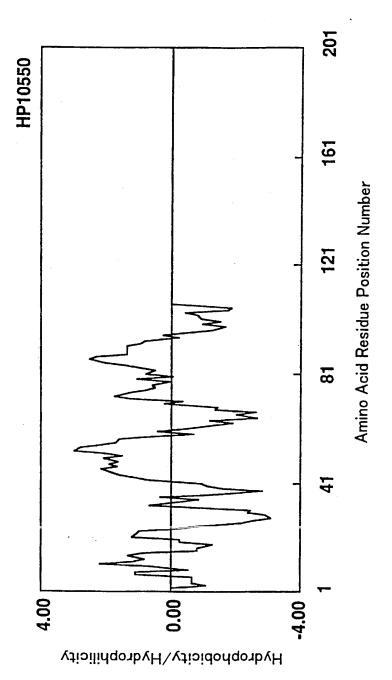
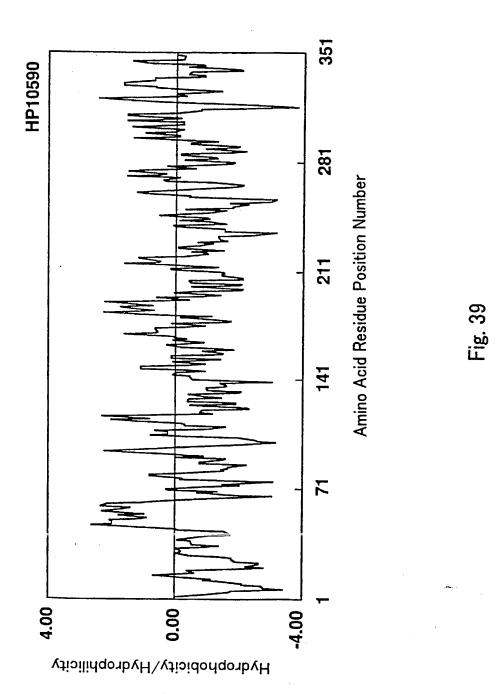


Fig. 38

WO 00/05367

39/50

PCT/JP99/03929



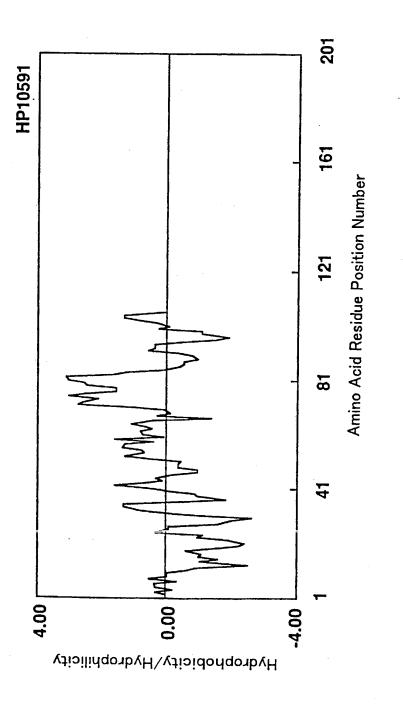


Fig. 40

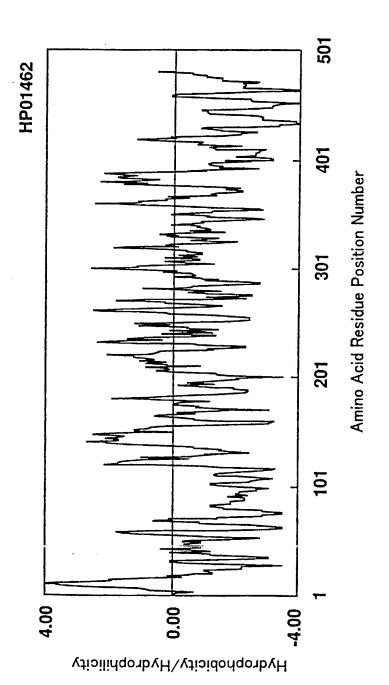


Fig. 41

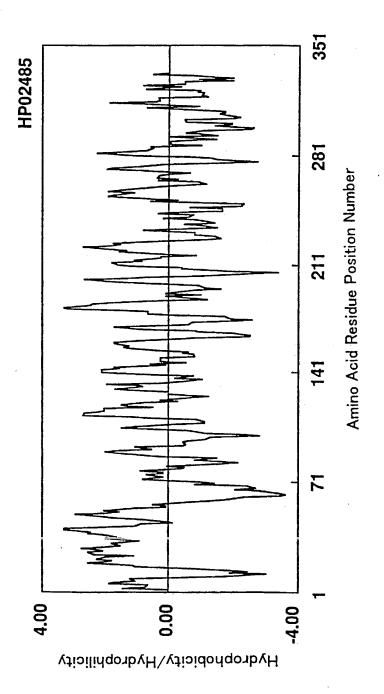


Fig.42

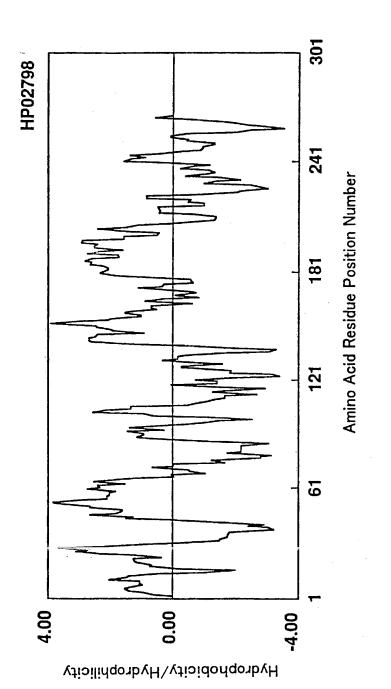
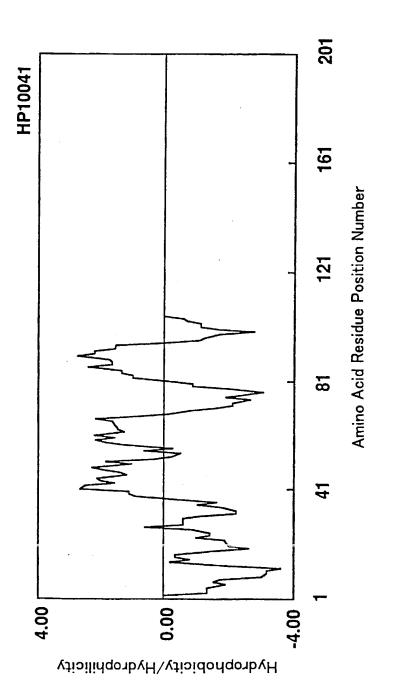
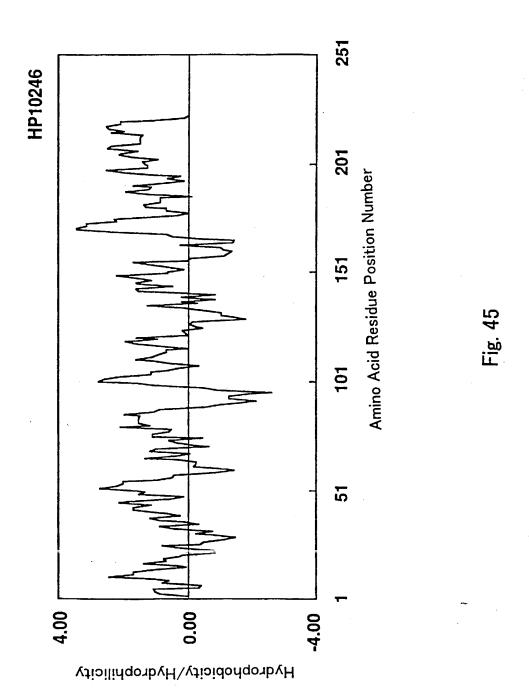


Fig. 43

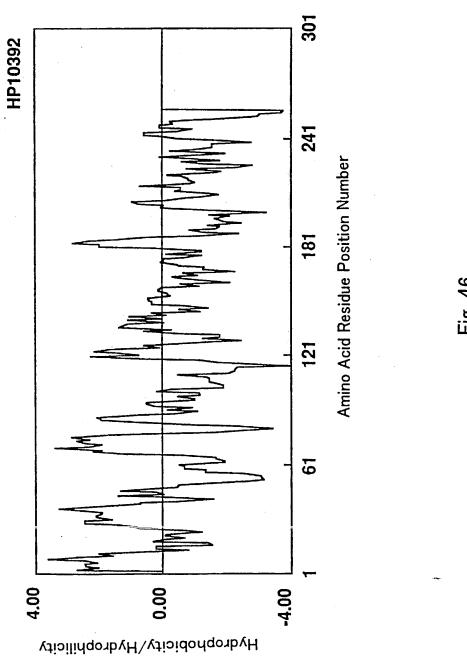


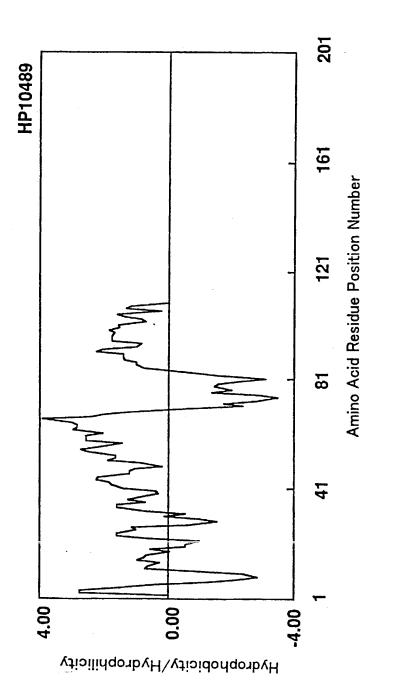
⊢lg. 44



PCT/JP99/03929

WO 00/05367





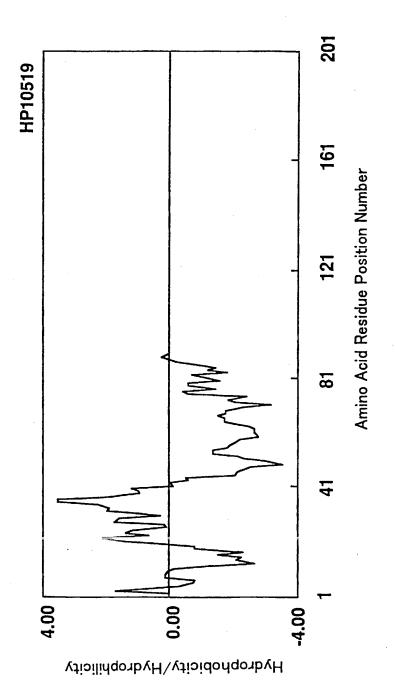
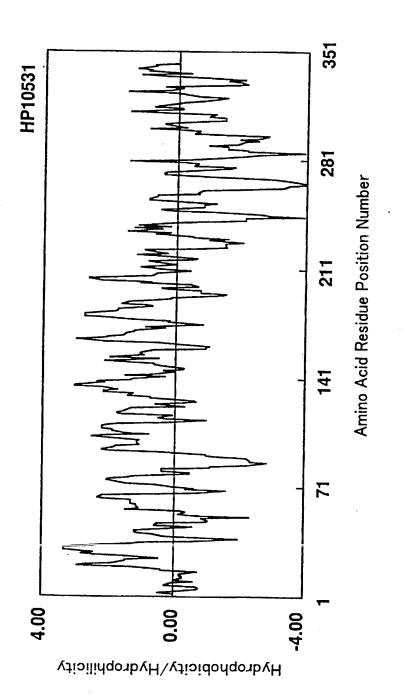


Fig. 48



0 7 ∐

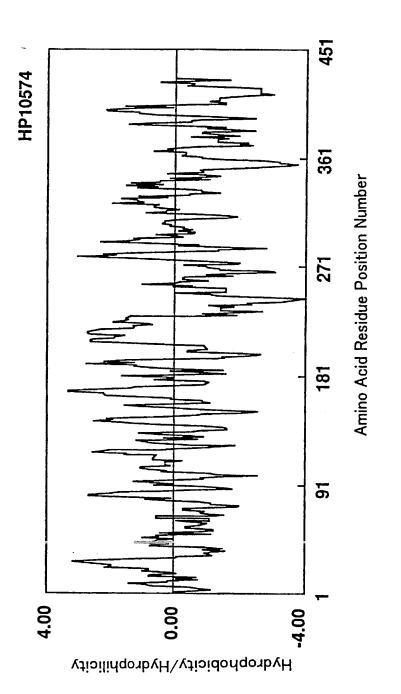


Fig. 50

Atty Docket No.: GIN-6718CP5US

DECLARATION, PETITION AND POWER OF ATTORNEY FOR PATENT APPLICATION

(Check one):

	Decl	aration Submitted with Initial Filing
×	Decl	aration Submitted after Initial Filing
As a b	elow	named inventor, I hereby declare that:
My re	sidenc	e, post office address and citizenship are as stated below next to my name,
origina	al, firs	m the original, first and sole inventor (if only one name is listed below) or an t and joint inventor (if plural names are listed below) of the subject matter which a patent is sought on the invention entitled:
		HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS
the spe	ecifica	tion of which (check one):
	is att	ached hereto.
	OI	3
×	was i	filed on 5 January 2001 as U.S. National Application Serial No. 09/743,247
	(U.S.	National Filing of PCT/JP99/03929 filed on 22 July 1999).
		and was amended by PCT Article 19 Amendment on(if applicable), and was amended by PCT Article 34 Amendment on
·		(if applicable).

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

PRIORITY CLAIM

(C)	heck	cone):
		no such applications have been filed.
	×	such applications have been filed as follows
1)	FO	REIGN PRIORITY CLAIM: I hereby claim for
Sta	tes (Code, §119(a)-(d) or §365(b) of any foreign appl

1) FOREIGN PRIORITY CLAIM: I hereby claim foreign priority benefits under Title 35, United
States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate or
§365(a) of any PCT international application which designated at least one country other than the
United States of America, listed below and have also identified below, by checking the box, any
foreign application for patent or inventor's certificate or any PCT international application having a
filing date before that of the application on which priority is claimed.
- II

Country	Foreign Filing	Priority	Certifi	ied Copy
	Date	Not Claimed		ached
	(dd/mm/yyyy)		Yes	No
JP	29/09/1998			×
JP	09/09/1998			×
JP	25/08/1998			×
JP	07/08/1998			×
JP	24/07/1998			×
	JP JP JP	Date (dd/mm/yyyy) JP 29/09/1998 JP 09/09/1998 JP 25/08/1998 JP 07/08/1998	Date (dd/mm/yyyy) JP 29/09/1998 □ JP 09/09/1998 □ JP 25/08/1998 □ JP 07/08/1998 □	Date (dd/mm/yyyy) Not Claimed Yes Att. Yes JP 29/09/1998 □ □ JP 09/09/1998 □ □ JP 25/08/1998 □ □ JP 07/08/1998 □ □

	Additional foreign application	numbers are listed on a supplementa	I priority sheet attached hereto.
--	--------------------------------	-------------------------------------	-----------------------------------

2) PROVISIONAL PRIORITY CLAIM: I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Provisional Application Number(s)	Filing Date (dd/mm/yyyy)

☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

3) <u>U.S./PCT PRIORITY CLAIM</u>: I hereby claim the benefit under Title 35, United States Code, §120 of any United States application or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Peter C. Lauro DeAnn F. Smith David J. Rikkers Chi Suk Kim Maria Laccotripe Zacharakis Debra J. Milasincic David R. Burns Sean D. Detweiler Peter S. Stecher Adam M. Goodmann Cynthia L. Kanik	Reg. No. 32,360 Reg. No. 36,683 Reg. No. 43,882 Reg. No. 42,728 Limited Recognition Under 37 C.F.R. § 10.9(b) Reg. No. 46,931 Reg. No. 46,590 Reg. No. 42,482 Reg. No. 47,259 Reg. No. 43,640 Reg. No. 37,320
Reg. No. 19,162 Reg. No. 24,798 Reg. No. 29,325 Reg. No. 31,503 Reg. No. 34,858 Reg. No. 33,505 Reg. No. 36,207 Reg. No. 38,220 Reg. No. 38,872 Reg. No. 17,425 Reg. No. 35,470 Reg. No. 41,710 Reg. No. 43,270 Reg. No. 36,397	Reg. No. 24,798 DeAnn F. Smith Reg. No. 29,325 David J. Rikkers Reg. No. 31,503 Chi Suk Kim Reg. No. 34,858 Maria Laccotripe Zacharakis Reg. No. 33,505 Debra J. Milasincic Reg. No. 38,220 David R. Burns Reg. No. 38,872 Sean D. Detweiler Reg. No. 17,425 Peter S. Stecher Reg. No. 35,470 Adam M. Goodmann Reg. No. 41,710 Cynthia L. Kanik Reg. No. 43,270
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Reg. No. 36,126

George Tarnowski

Michael R. Nagy

Reg. No. 27,472

Reg. No. 33,432

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Send Correspondence to: Amy E. Mandragouras, Esq., Lahive & Cockfield, LLP, 28 State Street, Boston, Massachusetts 02109, United States of America

Direct Telephone Calls to: Amy E. Mandragouras, Esq., (617) 227-7400, Lahive & Cockfield, LLP, 28 State Street, Boston, Massachusetts 02109, United States of America

Wherefore, I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Seishi KATO	
Inventor's signature Date	29. Mar. 2001
Residence	101/
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Citizenship	
Japan	ť
Post Office Address (if different)	

	Full name of sole or fir	st inventor		-
	Tomoko KIMURA	- Andrews - Landers - Land		
$\gamma (\lambda)$	Inventor's signature	Tomoko	Kimura	Date 27, Apr. 200/
1	Residence		Mary and the train of the same	1011
	715, 2-9-1, Kohoku, T	'suchiura-shi, Ibara	ki 300-0032, Japan	
	Citizenship			
	Japan			
	Post Office Address (if	different)		

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (dd/mm/yyyy)	Parent Patent Number (if applicable)
	PCT/JP99/03929	22 July 1999 (22.07.99)	

 \square Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.



PCTO9

ENTERED

RAW SEQUENCE LISTING

PATENT APPLICATION: US/09/743,247A

DATE: 11/19/2002 PG
TIME: 14:43:12

rinn, id.

Input Set : A:\sequence listing.txt

Output Set: N:\CRF4\11192002\I743247A.raw

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2 <110> APPLICANT: Sagami Chemical Research Center; Protegene Inc.
W-->
     3 <120> TITLE OF INVENTION: Human Proteins Having Hydrophobic Domains And DNAs Encoding
These
W--> 4
              Proteins
W--> 5 <130> FILE REFERENCE: 1997.13300
      6 <140> CURRENT APPLICATION NUMBER: US/09/743,247A
      7 <141> CURRENT FILING DATE: 1999-07-22
      8 <150> PRIOR APPLICATION NUMBER: JP 10-208820
      9 <151> PRIOR FILING DATE: 1998-07-24
     10 <150> PRIOR APPLICATION NUMBER: JP 10-224105
     11 <151> PRIOR FILING DATE: 1998-08-07
     12 <150> PRIOR APPLICATION NUMBER: JP 10-238116
     13 <151> PRIOR FILING DATE: 1998-08-25
     14 <150> PRIOR APPLICATION NUMBER: JP 10-254736
     15 <151> PRIOR FILING DATE: 1998-09-09
     16 <150> PRIOR APPLICATION NUMBER: JP 10-275505
     17 <151> PRIOR FILING DATE: 1998-09-29
W--> 18 <160> NUMBER OF SEQ ID: 150
     19 <170> SOFTWARE: Windows 95 (Word 98)
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     21 <211> LENGTH: 125
     22 <212> TYPE: PRT
     23 <213> ORGANISM: Homo sapiens
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     25 Met Ala Lys Tyr Leu Ala Gln Ile Ile Val Met Gly Val Gln Val Val
     26 1
                                             10
     27 Gly Arg Ala Phe Ala Arg Ala Leu Arg Gln Glu Phe Ala Ala Ser Arg
                     20
                                         25
     29 Ala Ala Ala Asp Ala Arg Gly Arg Ala Gly His Arg Ser Ala Ala Ala
                35
                                     40
                                                         4.5
     31 Ser Asn Leu Ser Gly Leu Ser Leu Gln Glu Ala Gln Gln Ile Leu Asn
            50.
                                 55
                                                     60
     33 Val Ser Lys Leu Ser Pro Glu Glu Val Gln Lys Asn Tyr Glu His Leu
                             70
     35 Phe Lys Val Asn Asp Lys Ser Val Gly Gly Ser Phe Tyr Leu Gln Ser
                         8.5
                                             90
    37 Lys Val Val Arg Ala Lys Glu Arg Leu Asp Glu Glu Leu Lys Ile Gln
                                        105
    39 Ala Gln Glu Asp Arg Glu Lys Gly Gln Met Pro His Thr
               115
                                    120
    41 <210> SEQ ID NO: 2
    42 <211> LENGTH: 131
    43 <212> TYPE: PRT
    44 <213> ORGANISM: Homo sapiens
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PATENT APPLICATION: US/09/743,247A

DATE: 11/19/2002 TIME: 14:43:12

Input Set : A:\sequence listing.txt
Output Set: N:\CRF4\11192002\1743247A.raw

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W--> 45 <400> SEQUENCE: 2
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    48 Gly Leu Met Phe Leu Met Leu Gly Cys Ala Leu Pro Ile Tyr Asn Lys
    49
                  20
                                     25
    50 Tyr Trp Pro Leu Phe Val Leu Phe Phe Tyr Ile Leu Ser Pro Ile Pro
              35
                                  40
    52 Tyr Cys Ile Ala Arg Arg Leu Val Asp Asp Thr Asp Ala Met Ser Asn
    53 50
                              55
                                                 60
    54 Ala Cys Lys Glu Leu Ala Ile Phe Leu Thr Thr Gly Ile Val Val Ser
                          70
                                             7.5
    56 Ala Phe Gly Leu Pro Ile Val Phe Ala Arg Ala His Leu Ile Glu Trp
                      85
                                         90
    58 Gly Ala Cys Ala Leu Val Leu Thr Gly Asn Thr Val Ile Phe Ala Thr
    59 100
                                 105
                                                    110
    60 Ile Leu Gly Phe Phe Leu Val Phe Gly Ser Asn Asp Asp Phe Ser Trp
                              120
    62 Gln Gln Trp
    63 130
    64 <210> SEQ ID NO: 3
    65 <211> LENGTH: 242
    66 <212> TYPE: PRT
    67 <213> ORGANISM: Homo sapiens
  -> 68 <400> SEQUENCE: 3
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    70 1
                        5
                                         10
    71 Lys Phe Lys Gly Pro Phe Thr Asp Val Val Thr Thr Asn Leu Lys Leu
                                     25
    73 Arg Asn Pro Ser Asp Arg Lys Val Cys Phe Lys Val Lys Thr Thr Ala
    74 35
    75 Pro Arg Arg Tyr Cys Val Arg Pro Asn Ser Gly Ile Ile Asp Pro Gly
                             55
    77 Ser Thr Val Thr Val Ser Val Met Leu Gln Pro Phe Asp Tyr Asp Pro
                         .70
    79 Asn Glu Lys Ser Lys His Lys Phe Met Val Gln Thr Ile Phe Ala Pro
                      8.5
                                         90
    81 Pro Asn Thr Ser Asp Met Glu Ala Val Trp Lys Glu Ala Lys Pro Asp
    82 100
                                 105
    83 Glu Leu Met Asp Ser Lys Leu Arg Cys Val Phe Glu Met Pro Asn Glu
    84 115
                                 120
                                         . 125
    85 Asn Asp Lys Leu Asn Asp Met Glu Pro Ser Lys Ala Val Pro Leu Asn
    86 130
                            135
                                                140
    87 Ala Ser Lys Gln Asp Gly Pro Met Pro Lys Pro His Ser Val Ser Leu
                         150
                                           .155
    89 Asn Asp Thr Glu Thr Arg Lys Leu Met Glu Glu Cys Lys Arg Leu Gln
                     165
                                        170
    91 Gly Glu Met Met Lys Leu Ser Glu Glu Asn Arg His Leu Arg Asp Glu
    92 180
                                 185
    93 Gly Leu Arg Leu Arg Lys Val Ala His Ser Asp Lys Pro Gly Ser Thr
```

PATENT APPLICATION: US/09/743,247A

DATE: 11/19/2002 TIME: 14:43:12

Input Set : A:\sequence listing.txt
Output Set: N:\CRF4\11192002\I743247A.raw

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195
                                200
    95 Ser Thr Ala Ser Phe Arg Asp Asn Val Thr Ser Pro Leu Pro Ser Leu
    96 210 215
    97 Leu Val Val Ile Ala Ala Ile Phe Ile Gly Phe Phe Leu Gly Lys Phe
    98 225
            230
                                            235
    99 Ile Leu
    100 <210> SEQ ID NO: 4
    101 <211> LENGTH: 264
    102 <212> TYPE: PRT
    103 <213> ORGANISM: Homo sapiens
W--> 104 <400> SEQUENCE: 4
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    106 1
                        5
    107 Leu Leu Met Pro Ala Val Ser Val Gly Asn Val Gly Gln Leu Ala Met
    108 20
                                      25
    109 Asp Leu Ile Ile Ser Thr Leu Asn Met Ser Lys Ile Gly Tyr Phe Tyr
    110 35
                                  40
    111 Thr Asp Cys Leu Val Pro Met Val Gly Asn Asn Pro Tyr Ala Thr Thr
                              5.5
    113 Glu Gly Asn Ser Thr Glu Leu Ser Ile Asn Ala Glu Val Tyr Ser Leu
                          70
                                            75
    115 Pro Ser Arg Lys Leu Val Ala Leu Gln Leu Arg Ser Ile Phe Ile Lys
                      85
                                         90
    117 Tyr Lys Ser Lys Pro Phe Cys Glu Lys Leu Leu Ser Trp Val Lys Ser
    118 100
                                    105
    119 Ser Gly Cys Ala Arg Val Ile Val Leu Ser Ser Ser His Ser Tyr Gln
    120 115
                       120
                                           125
    121 Arg Asn Asp Leu Gln Leu Arg Ser Thr Pro Phe Arg Tyr Leu Leu Thr
                             1.35
                                               140
    123 Pro Ser Met Gln Lys Ser Val Gln Asn Lys Ile Lys Ser Leu Asn Trp
                          150
                                            155
    125 Glu Glu Met Glu Lys Ser Arg Cys Ile Pro Glu Ile Asp Asp Ser Glu
                      165
                                         170
    127 Phe Cys Ile Arg Ile Pro Gly Gly Gly Ile Thr Lys Thr Leu Tyr Asp
                  180
                                     185
    129 Glu Ser Cys Ser Lys Glu Ile Gln Met Ala Val Leu Leu Lys Phe Val
    130 195
                                 200
    131 Ser Glu Gly Asp Asn Ile Pro Asp Ala Leu Gly Leu Val Glu Tyr Leu
                              215
                                                220
    133 Asn Glu Trp Leu Gln Ile Leu Lys Pro Leu Ser Asp Pro Thr Val
                         230
                                            235
    135 Ser Ala Ser Arg Trp Lys Ile Pro Ser Ser Trp Arg Leu Leu Phe Gly
                     245
    137 Ser Gly Leu Pro Pro Ala Leu Phe
    138
                  260
    139 <210> SEQ ID NO: 5
    140 <211> LENGTH: 112
    141 <212> TYPE: PRT
    142 <213> ORGANISM: Homo sapiens
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DATE: 11/19/2002 PATENT APPLICATION: US/09/743,247A TIME: 14:43:12

Input Set : A:\sequence listing.txt Output Set: N:\CRF4\11192002\I743247A.raw

```
W--> 143 <400> SEQUENCE: 5
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    145 1
                      5
                                         10
    146 Pro Gly Thr Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro
    147 20
                                     25
    148 Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp
    149 35
                                 40
    150 Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr
                             55
    151 50
                                                60
    152 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser
                           70
    154 Pro Trp Thr Ile Thr Gln Met Val Ile Gly Leu Ser Ile Ala Thr Trp
                                         90
                       85
    156 Gly Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala Tyr Arg Val Val
           100
    157
                              105
    158 <210> SEQ ID NO: 6
    159 <211> LENGTH: 146
    160 <212> TYPE: PRT
    161 <213> ORGANISM: Homo sapiens
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    163 Met Leu Ala Gly Ala Gly Arg Pro Gly Leu Pro Gln Gly Arg His Leu
    165 Cys Trp Leu Leu Cys Ala Phe Thr Leu Lys Leu Cys Gln Ala Glu Ala
    166 20
    167 Pro Val Glu Glu Glu Lys Leu Ser Ala Ser Thr Ser Asn Leu Pro Cys
    168 35
                                 40
    169 Trp Leu Val Glu Glu Phe Val Val Ala Glu Glu Cys Ser Pro Cys Ser
    170 50
                             55
                                                60
    171 Asn Phe Arg Ala Lys Thr Thr Pro Glu Cys Gly Pro Thr Gly Tyr Val
                          - 70
                                            7.5
    173 Glu Lys Ile Thr Cys Ser Ser Ser Lys Arg Asn Glu Phe Lys Ser Cys
                                         90
    175 Arg Ser Ala Leu Met Glu Gln Arg Leu Phe Trp Lys Phe Glu Gly Ala
    176 100
                                     105
    177 Val Val Cys Val Ala Leu Ile Phe Ala Cys Leu Val Ile Ile Arg Gln
    178 115
                                 120
    179 Arg Gln Leu Asp Arg Lys Ala Leu Glu Lys Val Arg Lys Gln Ile Glu
    180 130
                           135
                                                140
    181 Ser Ile
    182 145
    183 <210> SEQ ID NO: 7
    184 <211> LENGTH: 344
    185 <212> TYPE: PRT
    186 <213> ORGANISM: Homo sapiens
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    188 Met Asp Phe Leu Val Leu Phe Leu Phe Tyr Leu Ala Ser Val Leu Met
    189 1 5
                                10
    190 Gly Leu Val Leu Ile Cys Val Cys Ser Lys Thr His Ser Leu Lys Gly
                  20
                                     25
```

DATE: 11/19/2002 PATENT APPLICATION: US/09/743,247A TIME: 14:43:12

Input Set : A:\sequence listing.txt

Output Set: N:\CRF4\11192002\I743247A.raw

```
192 Leu Ala Arg Gly Gly Ala Gln Ile Phe Ser Cys Ile Ile Pro Glu Cys
  193 35
                                  40
  194 Leu Gln Arg Ala Val His Gly Leu Leu His Tyr Leu Phe His Thr Arg
                             55
  196 Asn His Thr Phe Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr
  197 65
                         70
  198 Thr Glu Tyr Thr Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu
                      85
                                         90
  200 Ser Leu His Tyr Leu Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu
                 100
                                    105
  202 Phe Phe Phe Thr Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys
       115
                                 120
                                                    125
  204 Ala Asn Glu Leu Leu Phe Leu His Val Tyr Glu Phe Asp Glu Val Met
  205 130
                             135
  206 Phe Pro Lys Asn Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala
                         150
  208 Arg Ser Lys His Cys Ser Val Cys Asn Trp Cys Val His Arg Phe Asp
                  165
                                     170
  210 His His Cys Val Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg
                180
                                  185
                                                       190
  212 Tyr Phe Leu Ile Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val
  213 195
                                 200
  214 Ala Ile Val Ser Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp
                            215
  216 Leu Tyr Gln Glu Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met
  217 225
                     230
                                           235
  218 Asp Thr Val Phe Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile
                     245
                                       250
  220 Val Phe Met Leu Gly Phe Val Val Leu Ser Phe Leu Leu Gly Gly
                                     265
  222 Tyr Leu Leu Phe Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn
  223
                                 280
                                                    285
  224 Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val
                             295
  226 Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser
                         310
                                            315
  228 His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro
                     325
                                        330
  230 Cys His Glu Arg Lys Lys Gln Glu
  232 <210> SEQ ID NO: 8
  233 <211> LENGTH: 97
  234 <212> TYPE: PRT
  235 <213> ORGANISM: Homo sapiens
-> 236 <400> SEQUENCE: 8
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  239 Gly Leu Glu Glu Lys Leu Ser Gln Cys Arg Arg Asp Leu Glu Ala Val
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RAW SEQUENCE LISTING ERROR SUMMARY PATENT APPLICATION: US/09/743,247A

DATE: 11/19/2002 TIME: 14:43:13

Input Set : A:\sequence listing.txt

Output Set: N:\CRF4\11192002\I743247A.raw

Please Note:

Use of n and/or Xaa have been detected in the Sequence Listing. Please review the Sequence Listing to ensure that a corresponding explanation is presented in the <220> to <223> fields of each sequence which presents at least one n or Xaa.

Seq#:93; Xaa Pos. 49
Seq#:113; Xaa Pos. 49

VERIFICATION SUMMARY

DATE: 11/19/2002 PATENT APPLICATION: US/09/743,247A TIME: 14:43:13

Input Set : A:\sequence listing.txt Output Set: N:\CRF4\11192002\I743247A.raw

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L:3 M:283 W: Missing Blank Line separator, <120> field identifier
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L:6 M:283 W: Missing Blank Line separator, <140> field identifier
L:18 M:283 W: Missing Blank Line separator, <160> field identifier
L:20 M:283 W: Missing Blank Line separator, <210> field identifier
L:24 M:283 W: Missing Blank Line separator, <400> field identifier
L:45 \ M:283 \ W: Missing Blank Line separator, <400> field identifier
L:68 M:283 W: Missing Blank Line separator, <400> field identifier
L:104 M:283 W: Missing Blank Line separator, <400> field identifier
L:143 M:283 W: Missing Blank Line separator, <400> field identifier
L:162 M:283 W: Missing Blank Line separator, <400> field identifier
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L:236 M:283 W: Missing Blank Line separator, <400> field identifier L:254 M:283 W: Missing Blank Line separator, <400> field identifier
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L:383 M:283 W: Missing Blank Line separator, <400> field identifier
L:394 M:283 W: Missing Blank Line separator, <400> field identifier
L:407 M:283 W: Missing Blank Line separator, <400> field identifier
L:430 M:283 W: Missing Blank Line separator, <400> field identifier
L:440 M:283 W: Missing Blank Line separator, <400> field identifier
L:452 M:283 W: Missing Blank Line separator, <400> field identifier
L:474 M:283 W: Missing Blank Line separator, <220> field identifier
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L:826 M:112 C: (48) String data converted to lower case,
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VERIFICATION SUMMARY

PATENT APPLICATION: US/09/743,247A

DATE: 11/19/2002 TIME: 14:43:13

Input Set : A:\sequence listing.txt

Output Set: N:\CRF4\11192002\I743247A.raw

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L:1155 M:283 W: Missing Blank Line separator, <400> field identifier
L:3363 M:257 W: Feature value mis-spelled or invalid, <221> Name/Key for SEQ ID#:93
L:3373 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:93 after pos.:48

L:4053 M:258 W: Mandatory Feature missing, <223> Tag not found for SEQ ID#:113 L:4053 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:113 after pos.:198

09/743247

WO 00/05367

PCT/JP99/03929

1/177 534 Rec'd PCT/PTO 0 5 JAN 2001

Sequence listing

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5 <120> Human Proteins Having Hydrophobic Domains And DNAs Encoding These Proteins

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10 <150> JP 10-208820

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<150> JP 10-224105

<151> 1998-08-07

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<150> JP 10-238116

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20 <151> 1998-09-09

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<151> 1998-09-29

25 <160> 150

<170> Windows 95 (Word 98)

<210> 1

30 <211> 125

<212> PRT

<213> Homo sapiens

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	Tyr	Trp	Pro	Leu	Phe	Val	Leu	Phe	Phe	Tyr	Ile	Leu		Pro	Ile	Pro
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	Tyr		Ile	Ala	Arg	Arg	Leu	Val	Asp	Asp	Thr		Ala	Met	Ser	Asn
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				100					105					110		
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	Ile	Leu														
10	~ 21	0> 4														
10		1> 26	5.4													
		2> PI														•
		3> Ho		sapie	ens											
				•												
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or.		Gly	Asn	Ser	Thr		Leu	Ser	Ile	Asn		Glu	Val	Tyr	Ser	Leu
25	65	_				70					75					80
	PLO	Ser	Arg	Lys		Val	Ālā	Leu	GIn		Arg	Ser	Ile	Phe		Lys
	Mrr-	T	Cam	T	85	5 1	a	01	•	90	•	0			95 -	_
	ıyı	Lys	Ser	100	PIO	Pne	cys	GIU		Leu	Leu	ser	TIP		ьys	ser
30	Ser	Gly	Cvc		Ara	1721	Tlo	17a 1	105	Sor	Sor	Sor	uic	110	Marr-	Cln
00	001	CLy	115	VIG	ALY	vaı	TTE	120	Ten	SeT	ser	Ser	125	ser	ıyı	GIII
	Ara	Asn		Len	Gln	T.em	Ara		Thr	Dro	Dhe	Δτα		T.e.it	T.ou	Thr
	9	130	P		11	ساند	135	JUL	1111	110	1116	140	* J +	ساتاس	Ten	THE
	Pro	Ser	Met	Gln	Lvs	Ser		Gln	Asn	Lvs	Ile		Ser	Leu	Asn	ጥተጥ
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	Ser Ala	Ser	Arg	Trp	Lys	Ile	Pro	Ser	Ser	Trp	Arg	Leu	Leu	Phe	Gly	
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6/177

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PCT/JP99/03929

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	His	His	Cys	Val	Trp	Val	Asn	Asn	Cys	Ile	Gly	Ala	Trp	Asn	Ile	Arg
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25			195					200					205			
	Āla	Ile	Val	Ser	Thr	Thr	Phe	Leu	Val	His	Leu	val	Val	Met	Ser	Asp
		210					215					220				
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	Val	Phe	Met	Leu	Gly	Phe	Val	Val	Val	Leu	Ser	Phe	Leu	Leu	Gly	Gly
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35			275					280					285			

8/177

Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val 295 300 Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser 310 315 5 His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro 325 330 335 Cys His Glu Arg Lys Lys Gln Glu 340 10 <210> 8 <211> 97 <212> PRT <213> Homo sapiens 15 Met Thr Lys Lys Lys Arg Glu Asn Leu Gly Val Ala Leu Glu Ile Asp 10 Gly Leu Glu Glu Lys Leu Ser Gln Cys Arg Arg Asp Leu Glu Ala Val 20 25 20 Asn Ser Arg Leu His Ser Arg Glu Leu Ser Pro Glu Ala Arg Arg Ser 40 Leu Glu Lys Glu Lys Asn Ser Leu Met Asn Lys Ala Ser Asn Tyr Glu 50 55 Lys Glu Leu Lys Phe Leu Arg Gln Glu Asn Arg Lys Asn Met Leu Leu 25 70 75 Ser Val Ala Ile Phe Ile Leu Leu Thr Leu Val Tyr Ala Tyr Trp Thr 85 Met 30 <210> 9 <211> 124 <212> PRT <213> Homo sapiens

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9/177

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	Arg	Val	Ala	Gly	Ala	Leu	Ile	Gly	Val	Leu	Leu	Gly	Val	Leu	Leu	Leu
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0.5	_		275			_		280			_		285	_	_	
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		290 	_				295			_		300	_,	_,	_,	_
	_	Phe	Leu	Glu	Arg	Pro	Ser	Ser	Ala	Ser		Val	Thr	Thr	Thr	_
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	gcaaaggagc	gcctggatga	ggaactcaaa	atccaggccc	aggaggacag	agaaaaaggg	360
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WO 00/05367

PCT/JP99/03929

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17/177

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WO 00/05367

PCT/JP99/03929

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	240	ber	Aid	ser	Arg		ьўs	lie	Pro			Trp	Arg	Leu	Lėü		
		5 cet				245		_4.4.			250		_ 4 _ 4		4-	255	
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,0	+-+-				260												
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PCT/JP99/03929

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WO 00/05367

PCT/JP99/03929

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	Ala Leu Met Glu Gln Arg Leu Phe Trp Lys Phe Glu Gly Ala Val Val	
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	Leu	Val	Leu	Gln	Gly	Met	Val	Tyr	Thr	Glu	Tyr	Thr	Trp	Glu	Val	Phe		
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	Gly	Tyr	Cys	Gln	Glu	Leu	Glu	Leu	Ser	Leu	His	Tyr	Leu	Leu	Leu	Pro		
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			_			_		Asp			_	-				*		
		170	•			_	175	•			•	180	•					
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WO 00/05367

PCT/JP99/03929

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	ĄzĄ	Leu	Gly	His	Leu	His	Val	Met	Asp	Thr	Val	Phe	Leu	Ile	Gln	Tyr		
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10	ctg	ttc	ctg	act	ttt	cca	cgg	att	gtc	ttc	atg	ctg	ggc	ttt	gtc	gtg		1122
	Leu	Phe	Leu	Thr	Phe	Pro	Arg	Ile	Val	Phe	Met	Leu	Gly	Phe	Val	Val		
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	Ala	Ala	Thr	Asn	Gln	Thr	Thr	Asn	Glu	Trp	Tyr	Arg	Gly	Asp	Trp	Ala		
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	Gln	Val	His	Arg	Asn	Ile	His	Ser	His	Gly	Leu	Arg	Ser	Asn	Leu	Gln		
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	Glu	Ile	Phe	Leu	Pro	Ala	Phe	Pro	Cys	His	Glu	Arg	Lys	Lys	Gln	Glu		
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PCT/JP99/03229

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WO 00/05367

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	Me	et Ti	hr Ly	ys Ly	ys L	ys Ai	rg Ci	lu A	sn L	eu G	ly V	al A	la L	eu G	lu I	le Asp	
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	Val Phe Lys Pro Asn Ser Lys Lys Arg Lys Ile Ser Leu Pro Ile Glu	
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	Asp Tyr Phe Asn Lys Gly Lys Asn Glu Pro Glu Asp Ser Lys Leu Arg	
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	Gly Gly Gln Ile Lys Leu Arg Glu Ile Pro Thr Ala Ala Leu Val Leu	
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WO 00/05367

### PCT/JP99/03929

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	Tyr	Thr	Asn	Gly	Leu	Gly	Leu	Ile	Asn	Leu	Thr	Val	Leu	Val	Pro	Pro	
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											gaa					-	779
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	Phe Leu Glu Arg Pro Ser Ser Ala Ser Thr Val Thr Thr Lys Ser	
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	Lys Asp Leu Gly Ile Trp His Val Pro Asn Lys Ser Pro Met Gln His	
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	225	-1-		V-1	*9	230		****		U_1	235				3	240
10		n an	N ~~	<i>c</i> 1	7		7 l n	7	210	T OIL		ם [ ת	Clar	Mot	7.50	
10	FIIE	WPII	ASII	GIU	-	ATG	ATG	ASII	ATG		Cys	ATG	σ⊥у	MEC	Arg	Vai
	_,	~ 1	_	_	245			•	_	250	_,	<b>~</b> 3	-1	-1	255	
	Thr	GIY	Cys		Thr	Glu	His	His	_	Пе	СТА	GTÄ	GIĀ	_	Tyr	Pne
				260					265		_		_	270		
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30				20					25		,			30		
	λen	Sar	) an		mh =	Dho	mh ~	Ton		בות	Clu	Gln.	Twe		Cue	Dhe
	vsh	Ser		Pile	THE	Pile	TIIL		PIO	Ara	GLY	GIII		Giu	Cys	File
	<b></b>	01.	35		_	_	_	40	_	_	-1		45		<b>~</b> 1.	
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### PCT/JP99/03929

80

### 33/177

70

75

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Arg Gln Leu Pro Ala
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His Trp Gly Val Phe
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	T.e.ii	) ra	Gln.		C1	C	Trp	T 011		17-1	) en	Gly	Glu.		Tla	M
	Ten	мц	355	Mec	стх	Ser	TIP	360	гуу	Val	Wali	GIY	365	ATA	TTG	TYF
5	Glu	Thr	His	Thr	Trp	Arq	Ser	Gln	Asn	Asp	Thr	Val	Thr	Pro	Asp	Val
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WO 00/05367

#### PCT/JP99/03929

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	Pro	Ser	Leu	Ser	His	Leu	Leu	Ser	Gln	Tyr	Tyr	Gly	Ala	Gly	Val	Ala
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	Arg	Asp	Pro	Gly	Phe	Arg	Ser	Asn	Phe	Arg	Arg	Gln	Asn	Gly	Ala	Ala
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WO 00/05367

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### 45/177

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PCT/JP99/03929 WO 00/05367

#### 46/177

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### 51/177

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PCT/JP99/03929

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WO 00/05367

### PCT/JP99/03929

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724

WO 00/05367 PCT/JP99/03929

#### 55/177

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WO 00/05367

# PCT/JP99/03929

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WO 00/05367

### PCT/JP99/03929

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WO 00/05367

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			35			-		40					45			
	Glu	Ile	Met	Ala	Asn	Asn	Phe	Ser	Leu	Glu	Ser	His	Asn	Ile	Ser	Leu
		50					55					60				
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#### PCT/JP99/03929

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	Asn	Ala	Val	Asn	Val	Thr	Trp	Lys	Lys	Asp	Gly	Glu	Gln	Leu	Glu	Asn
				100					105					110		
5	Asn	Tyr	Leu	Val	Ser	Ala	Thr	Gly	Ser	Thr	Leu	Tyr	Thr	Gln	Tyr	Arg
			115					120					125			
	Phe	Thr	Ile	Ile	Asn	Ser	Lys	Gln	Met	Gly	Ser	Tyr	Ser	Cys	Phe	Phe
		130					135					140				
	Arg	Glu	Glu	Lys	Glu	Gln	Arg	Gly	Thr	Phe	Asn	Phe	Lys	Val	Pro	Glu
10	145					150					155					160
	Leu	His	Gly	Lys	Asn	Lys	Pro	Leu	Ile	Ser	Tyr	Val	Gly	Asp	Ser	Thr
					165					170					175	
	Val	Leu	Thr	Cys	Lys	Cys	Gln	Asn	Cys	Phe	Pro	Leu	Asn	Trp	Thr	Trp
				180					185					190		
15	Tyr	Ser	Ser	Asn	Gly	Ser	Val	Lys	Val	Pro	Val	Gly	Val	Gln	Met	Asn
			195					200					205			
	Lys	Tyr	Val	Ile	Asn	Gly	Thr	Tyr	Ala	Asn	Glu	Thr	Lys	Leu	Lys	Ile
		210					215					220				
	Thr	Gln	Leu	Leu	Glu	Glu	Asp	Gly	Glu	Ser	Tyr	Trp	Cys	Arg	Ala	Leu
20	225					230					235					240
	Phe	Gln	T.eu	<b>~1</b>		_									_	Ser
			Ti-ca	GTA	Glu	Ser	Glu	Glu	His	Ile	Glu	Leu	Val	Val	Leu	DCI
			Deu	GIÀ	G1u 245	Ser	Glu	Glu	His	11e 250	Glu	Leu	Val	Val	Leu 255	DEI
	Tyr				245			Glu Phe		250					255	
	Tyr				245					250					255	
25		Leu	Val	Pro 260	245 Leu	Lys	Pro	Phe	Leu 265	250 Val	Ile	Val	Ala	Glu 270	255 Val	Ile
<b>2</b> 5		Leu	Val	Pro 260	245 Leu	Lys	Pro		Leu 265	250 Val	Ile	Val	Ala	Glu 270	255 Val	Ile
<b>2</b> 5	Leu	Leu Leu	Val Val 275	Pro 260 Ala	245 Leu Thr	Lys Ile	Pro Leu	Phe Leu 280	Leu 265 Cys	250 Val Glu	Ile Lys	Val Tyr	Ala Thr 285	Glu 270 Gln	255 Val Lys	Ile Lys
25	Leu	Leu Leu	Val Val 275	Pro 260 Ala	245 Leu Thr	Lys Ile	Pro Leu	Phe Leu	Leu 265 Cys	250 Val Glu	Ile Lys	Val Tyr	Ala Thr 285	Glu 270 Gln	255 Val Lys	Ile Lys
25	Leu Lys	Leu Leu Lys 290	Val Val 275 His	Pro 260 Ala Ser	245 Leu Thr	Lys Ile Glu	Pro Leu Gly 295	Phe Leu 280 Lys	Leu 265 Cys Glu	250 Val Glu Phe	Ile Lys Glu	Val Tyr Gln 300	Ala Thr 285 Ile	Glu 270 Gln Glu	255 Val Lys Gln	Ile Lys Leu
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	Leu Lys Lys 305	Leu Lys 290 Ser	Val Val 275 His	Pro 260 Ala Ser	245 Leu Thr Asp	Lys Ile Glu Asn 310	Pro Leu Gly 295 Gly	Phe Leu 280 Lys	Leu 265 Cys Glu	250 Val Glu Phe	lle Lys Glu Asn	Val Tyr Gln 300	Ala Thr 285 Ile	Glu 270 Gln Glu	255 Val Lys Gln	Ile Lys Leu Arg

PCT/JP99/03929

WO 00/05367

# 68/177

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	Thr	Leu	Gly	Gln	Ala	Pro	Arg	Gln	Lys	Gln	Gly	Ser	Thr	Gly	Glu	Glu
				20					25					30		
	Phe	His	Phe	Gln	Thr	Gly	Gly	Arg	Asp	Ser	Cys	Thr	Met	Arg	Pro	Ser
10			35					40					45			
	Ser	Leu	Gly	Gln	Gly	Ala	Gly	Glu	Val	Trp	Leu	Arg	Val	Asp	Cys	Arc
		50			•		55					60				
	Asn	Thr	Asp	Gln	Thr	Tyr	Trp	Cys	Glu	Tyr	Arg	Gly	Gln	Pro	Ser	Met
	65					70					75					80
15	Cys	Gln	Ala	Phe	Ala	Ala	Asp	Pro	Lys	Ser	Tyr	Trp	Asn	Gln	Ala	Leu
					85					90					95	
	Gln	Glu	Leu	Arg	Arg	Leu	His	His	Ala	Cys	Gln	Gly	Ala	Pro	Val	Leu
				100					105				i	110		
	Arg	Pro	Ser	Val	Cys	Arg	Glu	Ala	Gly	Pro	Gln	Ala	His	Met	Gln	Gln
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	Val	Thr	Ser	Ser	Leu	Lys	Gly	Ser	Pro	Glu	Pro	Asn	Gln	Gln	Pro	Glu
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	Ala	Gly	Thr	Pro	Ser	Leu	Arg	Pro	Lys	Ala	Thr	Val	Lys	Leu	Thr	Glu
	145					150					155					160
25	Ala	Thr	Gln	Leu	Gly	Lys	Asp	Ser	Met	Glu	Glu	Leu	Gly	Lys	Ala	Lys
					165					170					175	
	Pro	Thr	Thr	Arg	Pro	Thr	Ala	Lys	Pro	Thr	Gln	Pro	Gly	Pro	Arg	Pro
				180					185					190		
	Gly	Gly	Asn	Glu	Glu	Ala	Lys	Lys	Lys	Ala	Trp	Glu	His	Cys	Trp	Lys
30			195					200					205			
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<211> 48

#### 69/177

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	Trp	Leu	Gly	Ile	Leu	Ala	Thr	Ile	Ala	Gly	Leu	Val	Val	Val	Gly	Leu	
	145					150					155					160	
	Ala	Asp	Leu	Leu	Ser	Lys	His	Asp	Ser	Gln	His	Lys	Leu	Ser	Glu	Val	
					165					170					175		
5	Ile	Thr	Gly	Asp	Leu	Leu	Ile	Ile	Met	Ala	Gln	Ile	Ile	Val	Ala	Ile	
				180					185					190			
	Gln	Met	Val	Leu	Glu	Glu	Lys	Phe	Val	Tyr	Lys	His	Asn	Val	His	Pro	
			195					200					205				
	Leu	Arg	Ala	Val	Gly	Thr	Glu	Gly	Leu	Phe	Gly	Phe	Val	Ile	Leu	Ser	
10		210					215					220					
	Leu	Leu	Leu	Val	Pro	Met	Tyr	Tyr	Ile	Pro	Ala	Gly	Ser	Phe	Ser	Gly	
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	Asn	Pro	Arg	Gly	Thr	Leu	Glu	Asp	Ala	Leu	Asp	Ala	Phe	Cys	Gln	Val	
					245					250					255		
15	Gly	Gln	Gln	Pro	Leu	Ile	Ala	Val	Ala	Leu	Leu	Gly	Asn	Ile	Ser	Ser	
				260					265					270			
	Ile	Ala	Phe	Phe	Asn	Phe	Ala	Gly	Ile	Ser	Val	Thr	Lys	Glu	Leu	Ser	
			275	-				280					285				
~~	Ala		Thr	Arg	Met	Val	Leu	Asp	Ser	Leu	Arg	Thr	Val	Val	Ile	Trp	
20		290					295					300					
		Leu	Ser	Leu	Ala		Gly	Trp	Glu	Ala		His	Ala	Leu	Gln	Ile	
	305	_				310					315					320	
	Leu	Gly	Phe	Leu		Leu	Leu	Ile	Gly	Thr	Ala	Leu	Tyr	Asn	Gly	Leu	
0.5	•				325					330					335		
25	His	Arg	Pro		Leu	Gly	Arg	Leu		Arg	Gly	Arg	Pro	Leu	Ala	Glu	
		_		340	_				345					350			
	G1u	Ser		Gln	Glu	Arg	Leu	Leu	Gly	Gly	Thr	Arg	Thr	Pro	Ile	Asn	
	•		355					360					365				•
90	Asp	Ala	Ser														
30		370															
	٠٠ ٠٠	)	,														
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		l> 9(															
05		?> PI															
35	<213	s> Ho	omo s	apie	ens												

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5	Leu	Asn	Ser	Ile	Tyr	Gln	Cys	Pro	Glu	His	Ser	Gln	Leu	Thr	Thr	Leu
				20					25					30		
	Gly	Val	Asp	Gly	Lys	Glu	Phe	Pro	Glu	Val	His	Leu	Gly	Gln	Trp	Tyr
			35					40					45			
	Phe	Ile	Ala	Gly	Ala	Ala	Pro	Thr	Lys	Glu	Glu	Leu	Ala	Thr	Phe	Asp
10		50					55					60				
	Pro	Val	Asp	Asn	Ile	Val	Phe	Asn	Met	Ala	Ala	Gly	Ser	Ala	Pro	Met
	65					70					75					80
	Gln	Leu	His	Leu	Arg	Ala	Thr	Ile	Arg	Met						
					85					90						
15																
		)> 68														
	<21	1> 49	99													
		2> PI														
	<213	3> H	omo s	sapie	ens											
20			_													
		0> 68									_		_			
		Val	Asp	Arg	Gly	Pro	Leu	Leu	Thr		Ala	Ile	Ile	Phe	-	Leu
	1				5					10			_		15	·_
o E	ATE	TTE	GIÀ		Ala	Ile	Phe	Glu		Leu	G1u	GLu	Pro		Trp	Lys
25	<b>6</b> 5	<b>.</b>	<b>7</b>	20		_	_	_,	25	_			<b>-</b>	30	_	
	GIU	WIG		гàг	Asn	туг	Tyr		GIN	ьуѕ	ьеu	HIS		Leu	ьуѕ	GIU
	Dho	Dwa	35	•	<b>a</b> 1	<b>01</b> -	<b></b>	40	T		¥	<b>~1</b> ~	45	<b>63</b>	**- 1	**-7
	FILE	50	Cys	Leu	Gly	GIN	55	GIY	Leu	Asp	ьуѕ	60	Leu	GIU	vaı	val
30	Ser		פות	77-	c1	C1-	-	77-7	71-	т10	mh.∽	• • •	) cn	Cln	mh ~	Dho
00	65	nop	MIG	ита	Gly		GŢĀ	Val	Ата	TTE		Gly	ASII	GIII	THE	80
		Δen	מבנת	N con	m	70 Dra	n on	חות	Mot	Tlo	75 Pho	7 J -	בות	ጥ ኮ ≁	17-1	
	,	non	TTP	WPII	Trp 85	PLO	ASII	ATG	nec	90	riie.	VIG	Aid	1111		116
	ጥከተ	ጥኮ፦	716	G117	Tyr	G3v	y cz	Ual .	e F A		Tare	ጥኮታ	Dro	בומ	95 Gly	hr~
35			**6	100	- y -	Эту	VOII	val	105	110	-Ly S	T117		110	GLY	ALY

	Leu	Phe	Cys	Val	Phe	Tyr	Gly	Leu	Phe	Gly	Val	Pro	Leu	Cys	Leu	Thr
,			115					120					125			
	Trp	Ile	Ser	Ala	Leu	Gly	Lys	Phe	Phe	Gly	Gly	Arg	Ala	Lys	Arg	Leu
		130			•		135					140				
5	Gly	Gln	Phe	Leu	Thr	Lys	Arg	Gly	Val	Ser	Leu	Arg	Lys	Ala	Gln	Ile
	145					150					155					160
	Thr	Cys	Thr	Val	Ile	Phe	Ile	Val	Trp	Gly	Val	Leu	Val	His	Leu	Val
					165					170					175	
	Ile	Pro	Pro	Phe	Val	Phe	Met	Val	Thr	Glu	Gly	Trp	Asn	Tyr	Ile	Glu
10				180					185					190		
	Gly	Leu	Tyr	Tyr	Ser	Phe	Ile	Thr	Ile	Ser	Thr	Ile	Gly	Phe	Gly	Asp
			195					200					205			
	Phe		Ala	Gly	Val	Asn	Pro	Ser	Ala	Asn	Tyr	His	Ala	Leu	Tyr	Arg
. =		210					215					220				
15		Phe	Val	Glu	Leu	Trp	Ile	Tyr	Leu	Gly	Leu	Ala	Trp	Leu	Ser	
	225					230					235					240
	Phe	Val	Asn	Trp	Lys	Val	Ser	Met	Phe		Glu	Val	His	Lys		Ile
	_	_			245					250					255	
20	туs	Lys	Arg		Arg	Arg	Arg	Lys		Ser	Phe	Glu	Ser		Pro	His
20	<b>5</b>	•		260	_			_	265	_	_,	- <b>-</b>	_	270	_	
	Sei	Arg		ATa	Leu	GIN	Val	_	GIŸ	Ser	Tnr	Ата		Lys	Asp	Val
	<b>N</b> = m	77.	275	C	D1 -	<b>.</b>	<b>a</b>	280	<b>-</b>	<b>a</b> 1	<b>a</b> 1	m\	285	•	_	_
	ASII	290	Pne	ser	Phe	ren		Lys	ьys	GIU	GIU		TYE	Asn	Asp	Leu
25	Tle		Cln.	73.	C1	T	295	N 1	<b>W</b> -+	T	mh =	300	c1	<b>~</b> 1	01	<b></b>
20	305	пуъ	GTII	TTE	Gly	_	гĀг	AId	Mec	ьys	315	Ser	СТЙ	сту	GIÀ	
		Glv	Dro	Clar.	Pro	310	Lou	C1	Dro	Cln		C111	C311	Tou	Dro	320
	1111	GIŞ	FIO	GIÀ	325	СТА	теа	СТА	PLO	330	СТА	СТА	GIY	rea	335	WIG
	Leu	Pro	Pro	Sor	Leu	17a7	Dro	T 011	17al		T) T T T	Sor	Lve	Acn		tra l
30		110	110	340	пеа	vai	FLO	Leu	345	VAI	1 7 1.	SEL	Буз	350	ALG	vai
	Pro	Thr	T.en		Glu	Wa]	Ser	Gln		T.em	Ara	Ser	T.ve		uie.	<b>17</b> ⇒7
			355	O_Lu	GIU	vai	Der	360	111L	шец	my	Der	365	GLY	UTO	Vai
	Ser	Ara		Pro	Asp	Glu	Glu		₹7= T	λla	Δνα	λla		Glu	) en	Ser
		370			P	~_u	375	*3#C	- u.	u	9	380	- 10	- <u></u> u	יזיי	OCT
35	Ser		Ala	Pro	Glu	۲ <i>۵</i> ۲۶		Mot	) cn	Gln	T.eu		Δτα	Tle	Se~	Cl.
				110	Jiu	v ar	£ 116	1.1C.L	VOII	2711	⊒-cu	vah	n.y	エエニ	Ser	оти

	385					390					395					400
	Glu	Cys	Glu	Pro	Trp	Asp	Ala	Gln	Asp	туr	His	Pro	Leu	Ile	Phe	Gln
					405					410					415	
	Asp	Ala	Ser	Ile	Thr	Phe	Val	Asn	Thr	Glu	Ala	Gly	Leu	Ser	Asp	Glu
5				420					425					430		
	Glu	Thr	Ser	Lys	Ser	Ser	Leu	Glu	Asp	Asn	Leu	Ala	Gly	Glu	Glu	Ser
			435					440					445			
	Pro	Gln	Gln	Gly	Ala	Glu	Ala	Lys	Ala	Pro	Leu	Asn	Met	Gly	Glu	Phe
		450					455					460				
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	465					470					475					480
	Val	Pro	Tyr	Glu	Gln	Leu	Met	Asn	Glu	Tyr	Asn	Lys	Ala	Asn	Ser	Pro
					485			-		490					495	
	Lys	Gly	Thr													
15																
		> 69														
		1> 10														
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	-40															
		0> 69			-1		~7	_	_	_		_		•	<b>0</b> 1	
		Ala	ser	Ser	_	Ala	СТĀ	Asp	Pro		Asp	Ser	Lys	Arg	Gly	GIU
95	1	<b>5</b>			5	_	_,	_	_	10	_			<b>.</b>	15	_
25	Ala	Pro	Pne		GIn	Arg	Ile	Asp		Thr	Arg	GTI	Lys		Thr	Pro
	<b>~</b> 1	<b>03</b>	_	20	_		_		25		_	_ •		30	<b>a</b> 3-	
	GIU	GIN		HIS	ser	Met	_		Ala	GIU	Leu	Ala		Trp	Gln	гÀг
	**- 7	<b>.</b>	35	_	_	_		40	_	_•			45	_	-1	
20	val		Pro	Arg	Arg	Arg		Arg	Asn	Ile	Val		GIÀ	Leu	Gly	He
30		50	_			_	55		_			60				_
		Ala	Leu	Val	Leu		Ile	Tyr	Gly	Tyr		Phe	Tyr	Ser	Ile	
	65					70					75					80
	Gln	Glu	Arg	Phe		Asp	Glu	Leu	Glu	-	Glu	Ala	Lys	Ala	Ala	Arg
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#### PCT/JP99/03929

#### 74/177

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5	gttctcgcct	tctctttcct	ggatgagctt	cagaaggagt	tcattactac	ttataacatg	300
	atgaagacaa	atactgctgt	cagaccatac	tgtttcattg	aatttgataa	cttcattcag	360
	aggaccaagc	agcgatataa	taatcccagg	tctctttcaa	caaagataaa	tctttctgac	420
	atgcagacgg	aaatcaagct	gaggcctcct	tatcaaattt	ccatgtgcga	actggggtca	480
	gccaatggag	tcacatcage	attttctgtt	gactgtaaag	gtgctggtaa	gatttcttct	540
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	gatggtgatg	attttaatta	catcattgca	tttttccttg	gaacagcagc	ctgcctttac	720
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	tegetetace	cagtcggtta	cttggacaag	caagtgcctg	ataccagegt	gcaagagaca	180
	gaceggatee	tggtggagaa	gegetgetgg	gacategeet	tgggtcccct	caaacagatt	240
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0.5							

#### 76/177

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# 78/177.

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WO 00/05367

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35	35 40 45 50	

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30	gtc	ecct	cae t	tgca	gaaco	ec co	aggg	gcago	tgo	etgeo	aca	gaag	gatas	ca a	caco	caagt	1330
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	Gln Cys Pro Glu His Ser Gln Leu Thr Thr Leu Gly Val Asp Gly Lys	
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	Glu Phe Pro Glu Val His Leu Gly Gln Trp Tyr Phe Ile Ala Gly Ala	
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	Ala Pro Thr Lys Glu Glu Leu Ala Thr Phe Asp Pro Val Asp Asn Ile	
	55 60 65	
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25	Val Phe Asn Met Ala Ala Gly Ser Ala Pro Met Gln Leu His Leu Arg	
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	Ala Thr Ile Arg Met	
	90	
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	tggtgtt														180
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• •			-	_	-		_	ttc				-	_	-	-		789
10	Trp		Ser	Ala	Leu	СТĀ		Phe	Phe	GIA	Gly	_	Ala	Lys	Arg	Leu	
		130					135					140					
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	_	GIN	Pne	ьеи	Thr	_	Arg	Gly	vaı	ser		Arg	Lys	A1a	GIn		
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	TILL	Cys	1111	vai	165	FILE	116	vai	пр	170	vaı	Tierr	val	urs	175	Val	
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- <b>-</b>	aac	ctc	tac		tcc	ttc	atc	acc		tcc	acc	atc	aac		aat	gac	981
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	•		195	_				200					205		1		
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	Lys	Lys	Arg	Arg	Arg	Arg	Arg	Lys	Glu	Ser	Phe	Glu	Ser	Ser	Pro	His	
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	aac	atc	ttc	agc	ttt	ctt	tcc	aag	aag	gaa	gag	acc	tac	aac	gac	ctc	1269
5	Asn	Ile	Phe	Ser	Phe	Leu	Ser	Lys	Lys	Glu	Glu	Thr	Tyr	Asn	Asp	Leu	
		290					295					300					
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					325					330					335		
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		370					375					380					
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					405					410					415		
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	Val Pro Tyr Glu Gln L	eu Met Asn Glu Tyr Asr	n Lys Ala Asn Ser Pro	
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WO 00/05367

#### PCT/JP99/03929

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WO 00/05367

# PCT/JP99/03929

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WO 00/05367

#### PCT/JP99/03929

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#### 106/177

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WO 00/05367

#### PCT/JP99/03929

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WO 00/05367

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#### 111/177

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WO 00/05367 PCT/JP99/03929

112/177

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WO 00/05367

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PCT/JP99/03929

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WO 00/05367

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WO 00/05367

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WO 00/05367

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	Met Asn	

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	Ala	Tyr	Gln	Leu	Ser	Lys	Leu	Gly	Val	Ser	Leu	Val	Leu	Ser	Ala	Arg		
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	Arg	Val	His	Glu	Leu	Glu	Arg	Val	Lys	Arg	Arg	Cys		Glu	Asn	Gly		
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WO 00/05367

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	Ile	Ser	Met	Ala	Asn	Asp	Leu	Lys	Glu	Val	Trp	Ile	Ser	Glu	Gln	Pro	
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	Phe	Leu	Leu	Val	Thr	Tyr	Leu	Trp	Gln	Tyr	Met	Pro	Thr	Trp	Ala	Trp	
					295					300					305		
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	Trp	Ile	Thr	Asn	Lys	Met	Gly	Lys	Lys	Arg	Ile	Glu	Asn	Phe	Lys	Ser	
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	Gly	Val	Asp	Ala	Asp	Ser	Ser	Tyr	Phe	Lys	Ile	Phe			Lys	His	
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	Val	Ala	Ser	Glu	Asp	Gly	Ala	Leu	Arg	Ala	Pro	Glu	Ser	Gln	Ser	Val	
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	Ile	Gly	Leu	Gln	Val	Thr	Val	Pro	Phe	Met		Ala	Gly	Leu	Gly		
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	Lys	Gly	Asn	Leu	Glu	Met	Thr		Ala	Ser	Arg	Leu		Thr	ATA	ALA	
			115		. ,			120					125	۔ جانب		•	487
٥٣			gga														40/
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	Lys	Gln	Ser	Pro	Pro	Ile	Val	Lys	Ile	Leu	Lys	Phe	Gly	Trp	Phe	Pro	
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		290					295					300					
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	Lys	Thr	Val	Ser	Lys	Gln	Gln	Tyr	Lys	Gly	Met	Ala	Ile	Phe	Thr	Pro	
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	Ile	Ser	Thr	Tyr	Leu	His	Met	Trp	Ser	Ala	Pro	Gly	Val	Leu	Pro	Leu	
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	Gln	Met	Lys	Lys	Phe	Trp	Pro	Asn	Pro	Cys	Ser	Thr	Phe	Cys	Thr	Ser	
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	Thr	Trp		GIn	Ala	Leu	Asp		Asp	Asn	His	Cys		Pro	Tyr	Leu	
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20	THE	450	reu	GIĀ	Asp	Leu		GIY	The	сту	reu		Ald	Leu	Cys	Pue	
	++0		~~~			_+_	455					460				<b>.</b>	1/05
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	465	1111	nsp	ттЪ	Ten	470	БУЗ	ser	rys	Ата	475	ren	GTÅ	GTÀ	TTE	Ser	
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					Gly			Caac	999	,000	.cgcc	.99	c ca	ceeg	,	ccag	1330
				Ser	485	110	110										
	aatt	teet	ct c	acat		.a. aa	atac	- m	++0	actt	tat	ccct	taca	aa a	taat	tggga	1610
																cacac	1610 1670
35																ggett	1730
		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	-5 5	ישטיי			3~3~	Jugo	uut	~3~9		-944	u	y u	باحداد	gyett	×120

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	gee etg ge	a taa sa		+ 020 3			aad toa		158
							aag coo	. 900 900	130
05	MIG Dec MI				<b>ኮኮ</b> ተ ጥኮተ	Leu Ser	Lvs Ser	- Asp Ala	
2.3		_		T HTS .		Leu Ser	Lys Ser	Asp Ala	
25	aaa aaa gc	1	5		20			25	203
29	aaa aaa gc	1 c gec te	5 a aag ac	g ctg (	20 etg gag	aag agt	cag ttt	25 tca gat	203
20	aaa aaa gc Lys Lys Al	1 c gcc tc a Ala Se	5 a aag ac	g ctg (	20 etg gag Leu Glu	aag agt	cag ttt	25 tca gat Ser Asp	203
20	Lys Lys Al	1 c gcc tc a Ala Se 30	5 a aag ac r Lys Th	g ctg ( r Leu I	20 etg gag Leu Glu 35	aag agt Lys Ser	cag ttt Gln Phe	25 tca gat Ser Asp	<b>~</b> .
	Lys Lys Al	1 c gcc tc a Ala Se 30 g caa ga	5 a aag ac r Lys Th c egg gg	g ctg o r Leu I t ttg o	20 etg gag Leu Glu 35 gtg gtg	aag agt Lys Ser acg gac	cag ttt Gln Phe 40 ctc aaa	25 tca gat Ser Asp	203 ~ 254
30	Lys Lys Al	c gcc tc a Ala Se 30 g caa ga l Gln As	5 a aag ac r Lys Th c egg gg	g ctg o r Leu I t ttg o	20 etg gag Leu Glu 35 gtg gtg	aag agt Lys Ser acg gac	cag ttt Gln Phe 40 ctc aaa	25 tca gat Ser Asp	<b>~</b> .
	Lys Lys Al  aag ccg gt  Lys Pro Va	1 c gcc tc a Ala Se 30 g caa ga l Gln As	5 a aag ac r Lys Th c egg gg p Arg Gl	g ctg of Leu I t ttg of Leu V	20 ctg gag Leu Glu 35 gtg gtg	aag agt Lys Ser acg gac Thr Asp	cag ttt Gln Phe 40 ctc aaa Leu Lys	25 tca gat Ser Asp get gag Ala Glu	<b>~</b> .
	Lys Lys Al  aag ccg gt Lys Pro Va  4  agt gtg gt	c gcc tc a Ala Se 30 g caa ga l Gln As 5	5 a aag ac r Lys Th c egg gg p Arg Gl	g ctg of Leu I t ttg of y Leu I 50 c agc f	20 ctg gag Leu Glu 35 gtg gtg Val Val	aag agt Lys Ser acg gac Thr Asp tcg gca	cag ttt Gln Phe 40 ctc aaa Leu Lys 55 aag gcc	25 tca gat Ser Asp get gag Ala Glu cgg gac	254
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	Lys Lys Al  aag ccg gt Lys Pro Va  4  agt gtg gt Ser Val Va	c gcc tc a Ala Se 30 g caa ga l Gln As 5 t ctt ga l Leu Gl	a aag ac r Lys Th c egg gg p Arg Gl g eat eg u His Ar	g ctg of Leu I t ttg of Social Series	20 ctg gag Leu Glu 35 gtg gtg Val Val tac tgc	aag agt Lys Ser acg gac Thr Asp teg gca Ser Ala	cag titt Gln Phe 40 ctc aaa Leu Lys 55 aag gcc Lys Ala	25 E tca gat E Ser Asp E gct gag E Ala Glu E cgg gac E Arg Asp	254

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	His	Gly	Tyr	Asp	Val	Thr	Lys	Val	Phe	Gly	Ser	Lys	Phe	Thr	Gln	Ile		
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	Ser	Pro	Val	Trp	Leu	Gln	Leu	Lys	Arg	Arg	Gly	Arg	Glu	Met	Phe	Glu		
				110					115					120				
	gtc	acg	ggc	ctc	cac	gac	gtg	gac	caa	ggg	tgg	atg	cga	gct	gtc	agg		494
10	Val	Thr	Gly	Leu	His	Asp	Val	Asp	Gln	Gly	Trp	Met	Arg	Ala	Val	Arg		
			125					130					135					
					ggc													542
	Lys		Ala	Lys	Gly	Leu		Ile	Val	Pro	Arg		Leu	Phe	Glu	Asp		
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		Thr	Tyr	Asp	Asp		Arg	Asn	Val	Leu	165	ser	GIU	Asp	GIU	170		
	155	~~~				160	~+~	~+ ^	224	ata		220	227	cac	cet			638
					aag Lys													030
20	GIU	Giu	nea	per	175		Val	vai	GIII	180	, AIG	2,0	11011	· · · ·	185	1110		
20	gat	aac	ttc	ata	gtg	gag	atc	taa	aac		cta	cta	agc	caq		cqc		686
					Val													
	-	•		190				•	195					200	_			
	gtg	ggc	ata	atc	cac	atg	ctc	acc	cac	ttg	gcc	gag	gct	ctg	cac	cag		734
25	Val	Gly	Leu	Ile	His	Met	Leu	Thr	His	Leu	Ala	Glu	Ala	Leu	His	Gln		
			205					210					215					
	gcc	cgg	ctg	ctg	gcc	ctc	ctg	gtc	atc	ccg	cct	gcc	atc	acc	ccc	ggg		782
	Ala	Arg	Leu	Leu	Ala	Leu	Leu	Val	Ile	Pro	Pro	Ala	Ile	Thr	Pro	Gly	~.	
		220					225			•		230						
30	acc	gac	cag	ctg	ggc	atg	ttc	acg	cac	aag	gag	ttt	gag	cag	ctg	gcc		830
	Thr	Asp	Gln	Leu	Gly	Met	Phe	Thr	His	Lys	Glu	Phe	Glu	Gln	Leu	Ala		
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	ccc	gtg	ctg	gat	ggt	ttc	agc	ctc	atg	acc	tac	gac	tac	tct	aca	gcg		878
	Pro	Val	Leu	Asp	Gly	Phe	Ser	Leu	Met	Thr	Tyr	Asp	Tyr	Ser	Thr	Ala		
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WO 00/05367

#### PCT/JP99/03929

#### 132/177

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	Asp	Glu	Thr	Thr	Val	Glu	Leu	Glu	Gly	Gln	Asp	Glu	Asn	Gln	Glu	Gly	
20	65					70					75					80	
	Asp	Phe	Glu	Asp	Ala	Asp	Thr	Gln	Glu	Gly	Asp	Thr	Glu	Ser	Glu	Pro	
					85					90					95		
	Tyr	Asp	Asp	Glu	Glu	Phe	Glu	Gly	Tyr	Glu	Asp	Lys	Pro		Thr	Ser	
				100					105					110			
25	Ser	Ser	Lys	Asn	Lys	Asp	Pro	Ile	Thr	Ile	Val	Asp		Pro	Ala	His	
			115					120					125				
	Leu	Gln	Asn	Ser	Trp	Glu	Ser	Tyr	Tyr	Leu	Glu	Ile	Leu	Met	Val	Thr	
		130					135					140					
	Gly	Leu	Leu	Ala	Tyr	Ile	Met	Asn	Tyr	Ile		Gly	Lys	Asn	Lys		
30	145					150					155					160	
	Ser	Arg	Leu			Ala	Trp	Phe	Asn		His	Arg	Glu	Leu	Leu	Glu	
					165					170					175		
	Ser	Asn	Phe		Leu	Val	Gly	Asp		Gly	Thr	Asn	Lys		Ala	Thr	
				180					185			_		190			
35	Ser	Thr	Gly	Lys	Leu	Asn	Gln	Glu	Asn	Glu	His	Ile	Tyr	Asn	Leu	Trp	

#### PCT/JP99/03929

			195					200					205			
	Cys	Ser	Gly	Arg	Val	Cys	Cys	Glu	Gly	Met	Leu	Ile	Gln	Leu	Arg	Phe
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	Leu	Lys	Arg	Gln	Asp	Leu	Leu	Asn	Val	Leu	Ala	Arg	Met	Met	Arg	Pro
5	225					230					235					240
	Val	Ser	Asp	Gln	Val	Gln	Ile	Lys	Val	Thr	Met	Asn	Asp	Glu	Asp	Met
		•			245					250					255	
	Asp	Thr	Tyr	Val	Phe	Ala	Val	Gly	Thr	Arg	Lys	Ala	Leu	Val	Arg	Leu
				260					265					270		
10	Gln	Lys	Glu	Met	Gln	Asp	Leu	Ser	Glu	Phe	Cys	Ser	Asp	Lys	Pro	Lys
			275					280					285			
	Ser	Gly	Ala	Lys	Tyr	Gly	Leu	Pro	Asp	Ser	Leu	Ala	Ile	Leu	Ser	Glu
	,	290					295					300				
	Met	Gly	Glu	Val	Thr	Asp	Gly	Met	Met	Asp	Thr	Lys	Met	Val	His	Phe
15	305					310					315					320
	Leu	Thr	His	Tyr	Ala	Asp	Lys	Ile	Glu	Ser	Val	His	Phe	Ser	Asp	Gln
					325					330					335	
	Phe	Ser	Gly	Pro	Lys	Ile	Met	Gln	Glu	Glu	Gly	Gln	Pro	Leu	Lys	Leu
				340					345					350		
20	Pro	Asp	Thr	Lys	Arg	Thr	Leu	Leu	Phe	Thr	Phe	Asn	Val	Pro	Gly	Ser
			355					360					365			
	Gly	Asn	Thr	Tyr	Pro	Lys	Asp	Met	Glu	Ala	Leu	Leu	Pro	Leu	Met	Asn
		370					375					380				
	Met	Val	Ile	Tyr	Ser	Ile	Asp	Lys	Ala	Lys	Lys	Phe	Arg	Leu	Asn	Arg
25	385					390					395					400
	Glu	Gly	Lys	Gln	Lys	Ala	Asp	Lys	Àsn	Arg	Ala	Arg	Val	Glu	Glu	Asn
					405					410					415	
	Phe	Leu	Lys	Leu	Thr	His	Val	Gln	Arg	Gln	Glu	Ala	Ala		Ser	Arg
				420					425					430		
30	Arg	Glu	Glu	Lys	Lys	Arg	Ala	Glu	Lys	Glu	Arg	Ile	Met	Asn	Glu	Glu
			435					440					445			
	Asp	Pro	Glu	Lys	Gln	Arg	Arg	Leu	Glu	Glu	Ala	Ala	Leu	Arg	Arg	Glu
		450					455					460				
	Gln	Lys	Lys	Leu	Glu	Lys	Lys	Gln	Met	Lys	Met	Lys	Gln	Ile	Lys	Val
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	<21	1> 3:	34													
5	<21	2> PI	RТ													
	<21	3> H	omo s	sapie	ence											
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	Thr	Leu	Ala	Val	Leu	Gln	Phe	Val	Phe	Ser	Phe	Leu	Ala	Leu	Ala	Gl
				20					25					30		
	Ile	Cys	Thr	Val	Gly	Phe	Ile	Ala	Leu	Leu	Phe	Thr	Arg	Phe	Trp	Le
			35					40					45			
15	Leu	Thr	Val	Leu	Tyr	Ala	Ala	Trp	Trp	Tyr	Leu	Asp	Arg	Asp	Lys	Pro
		50					55					60				
	Arg	Gln	Gly	Gly	Arg	His	Ile	Gln	Ala	Ile	Arg	Cys	Trp	Thr	Ile	Tr
	65					70					75					80
	Lys	Tyr	Met	Lys	Asp	Tyr	Phe	Pro	Ile	Ser	Leu	Val	Lys	Thr	Ala	Gl
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	Leu	Asp	Pro	Ser	Arg	Asn	Tyr	Ile	Ala	Gly	Phe	His	Pro	His	Gly	Va.
				100					105					110		
	Leu	Ala	Val	Gly	Ala	Phe	Ala	Asn	Leu	Cys	Thr	Glu	Ser	Thr	Gly	Phe
			115					120					125			
25	Ser	Ser	Ile	Phe	Pro	Gly	Ile	Arg	Pro	His	Leu	Met	Met	Leu	Thr	Let
		130					135					140				
	Trp	Phe	Arg	Ala	Pro	Phe	Phe	Arg	Asp	Tyr	Ile	Met	Ser	Ala	Gly	Let
	145					150					155					160
	Val	Thr	Ser	Glu	Lys	Glu	Ser	Ala	Ala	His	Ile	Leu	Asn	Arg	Lys	Gly
30					165					170					175	
	Gly	Gly	Asn	Leu	Leu	Gly	Ile	Ile	Val	Gly	Gly	Ala	Gln	Glu	Ala	Let
		•		180					185					190		
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			195					200					205			
35	Phe	Val	Arg	Leu	Ala	Leu	Thr	His	Gly	Ala	Pro	Leu	Val	Pro	Ile	Phe

#### 142/177

215 220 210 Ser Phe Gly Glu Asn Asp Leu Phe Asp Gln Ile Pro Asn Ser Ser Gly 230 235 Ser Trp Leu Arg Tyr Ile Gln Asn Arg Leu Gln Lys Ile Met Gly Ile 5 250 245 Ser Leu Pro Leu Phe His Gly Arg Gly Val Phe Gln Tyr Ser Phe Gly 265 Leu Ile Pro Tyr Arg Arg Pro Ile Thr Thr Val Val Gly Lys Pro Ile 280 10 Glu Val Gln Lys Thr Leu His Pro Ser Glu Glu Glu Val Asn Gln Leu 290 295 300 His Gln Arg Tyr Ile Lys Glu Leu Cys Asn Leu Phe Glu Ala His Lys 310 315 Leu Lys Phe Asn Ile Pro Ala Asp Gln His Leu Glu Phe Cys 15 325 330 <210> 123 <211> 267 <212> PRT 20 <213> Homo sapience <400> 123 Met Ala Pro Trp Ala Leu Leu Ser Pro Gly Val Leu Val Arg Thr Gly 10 25 His Thr Val Leu Thr Trp Gly Ile Thr Leu Val Leu Phe Leu His Asp 25 Thr Glu Leu Arg Gln Trp Glu Glu Gln Gly Glu Leu Leu Pro Leu 40 45 Thr Phe Leu Leu Leu Val Leu Gly Ser Leu Leu Leu Tyr Leu Ala Val 30 55 Ser Leu Met Asp Pro Gly Tyr Val Asn Val Gln Pro Gln Pro Gln Glu 70 Glu Leu Lys Glu Glu Gln Thr Ala Met Val Pro Pro Ala Ile Pro Leu 90 35 Arg Arg Cys Arg Tyr Cys Leu Val Leu Gln Pro Leu Arg Ala Arg His

#### 143/177

Cys Arg Glu Cys Arg Arg Cys Val Arg Arg Tyr Asp His His Cys Pro Trp Met Glu Asn Cys Val Gly Glu Arg Asn His Pro Leu Phe Val Val Tyr Leu Ala Leu Gln Leu Val Val Leu Leu Trp Gly Leu Tyr Leu Ala Trp Ser Gly Leu Arg Phe Phe Gln Pro Trp Gly Leu Trp Leu Arg Ser Ser Gly Leu Leu Phe Ala Thr Phe Leu Leu Ser Leu Phe Ser Leu Val Ala Ser Leu Leu Leu Val Ser His Leu Tyr Leu Val Ala Ser Asn Thr Thr Trp Glu Phe Ile Ser Ser His Arg Ile Ala Tyr Leu Arg Gln Arg Pro Ser Asn Pro Phe Asp Arg Gly Leu Thr Arg Asn Leu Ala His Phe Phe Cys Gly Trp Pro Ser Gly Ser Trp Glu Thr Leu Trp Ala Glu Glu Glu Glu Gly Ser Ser Pro Ala Val <210> 124 <211> 106 <212> PRT <213> Homo sapience <400> 124 Met Ser Thr Asn Asn Met Ser Asp Pro Arg Arg Pro Asn Lys Val Leu Arg Tyr Lys Pro Pro Pro Ser Glu Cys Asn Pro Ala Leu Asp Asp Pro Thr Pro Asp Tyr Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Sex

# PCT/JP99/03929

		50					55					60				
	Phe	Ile	Ser	Phe	Ala	Asn	Ser	Arg	Ser	Ser	Glu	Asp	Thr	Lys	Gln	Met
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	Met	Ser	Ser	Phe	Met	Leu	Ser	Ile	Ser	Ala	Val	Val	Met	Ser	Tyr	Leu
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	1				5					10					15	
	Tyr	Phe	Ile	Thr	Tyr	Lys	Cys	Ser	Gly	Leu	Ser	Glu	Tyr	Asn	Ala	Phe
				20					25					30		
	Trp	Lys	Cys	Val	Gln	Ala	Gly	Val	Thr	Tyr	Leu	Phe		Gln	Leu	Cys
20			35					40					45			
	Lys		Leu	Phe	Leu	Ala		Phe	Phe	Pro	Thr	•	GLu	Gly	GTA	Ile
		50					55			_		60				_
	Tyr	Asp	Phe	Ile	Gly	Glu	Phe	Met	Lys	Ala		Val	Asp	Val	Ala	
	65					70	_				75 -	.,	<b>a</b> 1	•	<b>0</b> 1	80
25	Leu	Ile	Gly	Leu		Leu	Val	Met	Ser		Asn	Ala	GIY	Lys		GIU
			_		85			_		90		mh		<b>63</b>	95	T1.
	Tyr	Lys	Ile		Val	Ala	Ala	Leu		Trp	AIA	THE	Ala	Glu	ьеu	TTE
				100				_	105				01	110	<b>~</b> 2	Dha
00	Met	Ser			Ile	Pro	Leu		Val	GIY	ATA	Arg		Ile	GIU	Pne
30			115					120		_	_	_	125	C	<b>T</b>	**-1
	Asp			Tyr	Ile	Gln		Ser	Ile	Asp	Ser		TTE	Ser	Leu	vai
		130					135		_	_		140	1	<b>.</b>	<b></b>	
			Ile	Val	Ala		Ala	Gln	Val	Trp		Ile	Thr	Arg	туг	
	145					150					155			_,	_	160
35	Leu	Tyr	His	Thr	Phe	Arg	Pro	Ala	Val	Leu	Leu	Leu	Met	Phe	Leu	Ser

					165					170					175	
	Val	Tyr	Lys	Ala	Phe	Val	Met	Glu	Thr	Phe	Val	His	Leu	Cys	Ser	Leu
				180					185					190		
	Gly	Ser	Trp	Ala	Ala	Leu	Leu	Ala	Arg	Ala	Val	Val	Thr	Gly	Leu	Leu
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	<213	3> H	omo s	sapie	ence											
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ė	1				5					10					15	
	Leu	Ser	Arg	Trp	Leu	Ala	Gln	Pro	Tyr	Tyr	Leu	Leu	Ser	Ala	Leu	Leu
				20					25					30		
	Ser	Ala	Ala	Phe	Leu	Leu	Val	Arg	Lys	Leu	Pro	Pro	Leu	Cys	His	Gly
20			35					40					45			
	Leu	Pro	Thr	Gln	Arg	Glu	Asp	Gly	Asn	Pro	Cys	Asp	Phe	Asp	Trp	Arg
		50					55					60				
	Glu	Val	Glu	Ile	Leu	Met	Phe	Leu	Ser	Ala	Ile	Val	Met	Met	Lys	Asn
	65					70					75					80
25	Arg	Arg	Ser	Met	Phe	Leu	Met	Thr	Cys	Lys	Pro	Pro	Leu	Tyr	Met	Gly
					85					90					95	
	Pro	Glu	Tyr	Ile	Lys	Tyr	Phe	Asn	Asp	Lys	Thr	Ile	Asp	Glu	Glu	Leu
				100					105					110		
	Glu	Arg	Asp	Lys	Arg	Val	Thr	Trp	Ile	Val	Glu	Phe	Phe	Ala	Asn	Trp
30			115					120					125			
	Ser	Asn	Asp	Cys	Gln	Ser	Phe	Ala	Pro	Ile	Tyr	Ala	Asp	Leu	Ser	Leu
		130					135					140				
	Lys	Tyr	Asn	Cys	Thr	Gly	Leu	Asn	Phe	Gly		Val	Asp	Val	Gly	Arg
	145					150					155					160
35	Tyr	Thr	Asp	Val	Ser	Thr	Arg	Tyr	Lys	Val	Ser	Thr	Ser	Pro	Leu	Thr

# 146/177

Lys Gln Leu Pro Thr Leu Ile Leu Phe Gln Gly Gly Lys Glu Ala Metala 180	ne In In
Arg Arg Pro Gln Ile Asp Lys Lys Gly Arg Ala Val Ser Trp Thr Ph  5	ln ln lo
5	ln ln lo
Ser Glu Glu Asn Val Ile Arg Glu Phe Asn Leu Asn Glu Leu Tyr Gl 210 215 220  Arg Ala Lys Lys Leu Ser Lys Ala Gly Asp Asn Ile Pro Glu Glu Gl 225 230 235 24  10 Pro Val Ala Ser Thr Pro Thr Thr Val Ser Asp Gly Glu Asn Lys Ly 245 250 255  Asp Lys <pre> <pre> <pre></pre></pre></pre>	Ln 10
210 215 220  Arg Ala Lys Lys Leu Ser Lys Ala Gly Asp Asn Ile Pro Glu Glu Glu 225 230 230 235 235 24  10 Pro Val Ala Ser Thr Pro Thr Thr Val Ser Asp Gly Glu Asn Lys Lys 245 250 250 255  Asp Lys 210> 127  15 <211> 110	Ln 10
Arg Ala Lys Lys Leu Ser Lys Ala Gly Asp Asn Ile Pro Glu Glu Glu 225 230 235 24  10 Pro Val Ala Ser Thr Pro Thr Thr Val Ser Asp Gly Glu Asn Lys Ly 245 250 255  Asp Lys 220 250 255  Asp Lys 210> 127  15 <211> 110	10
225 230 235 24  10 Pro Val Ala Ser Thr Pro Thr Thr Val Ser Asp Gly Glu Asn Lys Ly 245 250 255  Asp Lys <pre> <pre> <pre></pre></pre></pre>	10
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245 250 255 Asp Lys  <210> 127  15 <211> 110  <212> PRT  <213> Homo sapience  <400> 127	7S
Asp Lys <pre> &lt;210&gt; 127  15</pre>	
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	u
1 5 10 15	
Ala Ala Val Arg Gly Asn Ala Ala Val Leu Asp Tyr Cys Arg Thr Sei	r
20 25 30	
Val Ser Ala Leu Ser Gly Ala Thr Ala Gly Ile Leu Gly Leu Thr Gly 25 40 45	У
Leu Tyr Gly Phe Ile Phe Tyr Leu Leu Ala Ser Val Leu Leu Ser Leu 50 55 60	ц
50 55 60  Leu Leu Ile Leu Lys Ala Gly Arg Arg Trp Asn Lys Tyr Phe Lys Sen	
30 Arg Arg Pro Leu Phe Thr Gly Gly Leu Ile Gly Gly Leu Phe Thr Ty	
85 90 95	_
Val Leu Phe Trp Thr Phe Leu Tyr Gly Met Val His Val Tyr	
100 105 110	
100 100 110	

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<210> 128

35

#### PCT/JP99/03929

#### 147/177

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Arg Ile Phe Glu Arg Arg Tyr Gly Ser Arg Lys Phe Ala Ser Phe Leu

					85					90					95	
	Leu	Gly	Ser	Trp	Val	Leu	Ser	Ala	Leu	Phe	Asp	Phe	Leu	Leu	Ile	Glu
				100					105					110		
	Ala	Met	Gln	Tyr	Phe	Phe	Gly	Ile	Thr	Ala	Ala	Ser	Asn	Leu	Pro	Ser
5			115					120					125			
	Gly	Phe	Leu	Ala	Pro	Val	Phe	Ala	Leu	Phe	Val	Pro	Phe	Tyr	Cys	Ser
		130					135					140				
	Ile	Pro	Arg	Val	Gln	Val	Ala	Gln	Ile	Leu	Gly	Pro	Leu	Ser	Ile	Thr
	145					150					155					160
10	Asn	Lys	Thr	Leu	Ile	Tyr	Ile	Leu	Gly	Leu	Gln	Leu	Phe	Thr	Ser	Gly
					165					170					175	
	Ser	Tyr	Ile	Trp	Ile	Val	Ala	Ile	Ser	Gly	Leu	Met	Ser	Gly	Leu	Cys
				180					185					190		
	Tyr	Asp	Ser	Lys	Met	Phe	Gln	Val	His	Gln	Val	Leu	Cys	Ile	Pro	Ser
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	Trp	Met	Ala	Lys	Phe	Phe	Ser	Trp	Thr	Leu	Glu	Pro	Ile	Phe	Ser	Ser
		210					215					220				
		Glu	Pro	Thr	Ser		Ala	Arg	Ile	Gly	Met	Gly	Ala	Thr	Leu	Asp
20	225					230					235					240
20	Ile	Gln	Arg	Gln		Arg	Met	Glu	Leu		Asp	Arg	Gln	Leu		Phe
	_			_	245					250			_	_	255	
	Ser	GIn	Phe		Gln	Gly	Arg	Arg		Arg	Gln	Gln	Gln	Gly	Gly	Met
	-1.	•	_	260	_	_	_,	_	265	_			_	270		
25	шe	ASI	_	Asn	Arg	Leu	Pne		Pro	Leu	Arg	GIN	_	Gln	Asn	Val
20	<b>1</b>	Me	275		<b>0</b> 3	•	<b>01</b>	280	<b>01</b>	<b>.</b>			285	_		
	ASN	290	GIN	GTÀ	GIĀ	Arg		ser	GIU	Pro	Ala		Pro	Pro	reu	GIU
	17n l		<b>~1</b>	<b>a</b> 1	<b>~</b> 1~	**- 1	295	•	T	24-6	<b>a</b> 1	300	<b>a</b> 1	DL -	<b>0</b>	<b>.</b>
	305	Ser	GIU	GIU	GIN		Ala	Arg	Leu	Met		Met	сту	Pne	ser	Arg ~
30		A en	<b>7.7</b> m	T 011	C1	310	T 011	2	*1~	Co~	315	N ===	N	T	<b>1</b> - n	320
	сту	roh	wra	neu	325	WIG	ьeu	arg	ATG	330	ASI	ASN	Asp	Leu		val
	Δla	ጥኮኮ	Aen	Dho	Leu	Len	C1=	u:-		330					335	
	, <u></u> u	****	นอบ	340	TICK	TIEU	GIII	UTS								
				240												

# 149/177

<211> 428

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	<21	3> Ho	omo s	sapie	ence											
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	Met	Gly	Pro	Pro	Pro	Gly	Ala	Gly	Val	Ser	Cys	Arg	Gly	Gly	Cys	Gly
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				20					25					30		
10	Ala	Pro	Gly	Ser	Arg	Gly	Ala	Glu	Ala	Val	Trp	Thr	Ala	Tyr	Leu	Asn
			35					40					45			
	Val	Ser	Trp	Arg	Val	Pro	His	Thr	Gly	Val	Asn	Arg	Thr	Val	Trp	Glu
		50					55					60				
	Leu	Ser	Glu	Glu	Gly	Val	Tyr	Gly	Gln	Asp	Ser	Pro	Leu	Glu	Pro	Val
15	65					70					75					80
	Ala	Gly	Val	Leu	Val	Pro	Pro	Asp	Gly	Pro	Gly	Ala	Leu	Asn	Ala	Cys
					85			•		90					95	
	Asn	Pro	His	Thr	Asn	Phe	Thr	Val	Pro	Thr	Val	Trp	Gly	Ser	Thr	Val
				100					105					110		
20	Gln	Val	Ser	Trp	Leu	Ala	Leu	Ile	Gln	Arg	Gly	Gly	Gly	Cys	Thr	Phe
			115					120					125			
	Ala	Asp	Lys	Ile	His	Leu	Ala	Tyr	Glu	Arg	Gly	Ala	Ser	Gly	Ala	Val
		130					135					140				
	Ile	Phe	Asn	Phe	Pro	Gly	Thr	Arg	Asn	Glu	Val	Ile	Pro	Met	Ser	His
25	145					150					155					160
	Pro	Gly	Ala	Val	Asp	Ile	Val	Ala	Ile	Met	Ile	Gly	Asn	Leu	Lys	Gly
					165					170					175	
	Thr	Lys	Ile	Leu	Gln	Ser	Ile	Gln	Arg	Gly	Ile	Gln	Val	Thr	Met	Val ⁻
				180					185					190		
30	Ile	Glu	Val	Gly	Lys	Lys	His	Gly	Pro	$\mathtt{Trp}$	Val	Asn	His	Tyr	Ser	Ile
			195					200					205			
	Phe	Phe	Val	Ser	Val	Ser	Phe	Phe	Ile	Ile	Thr	Ala	Ala	Thr	Val	Gly
		210					215					220				
	Tyr	Phe	Ile	Phe	Tyr	Ser	Ala	Arg	Arg	Leu	Arg	Asn	Ala	Arg	Ala	Gln
35	225					230					235					240

	Ser	Arg	Lys	Gln	Arg	Gln	Leu	Lys	Ala	Asp	Ala	Lys	Lys	Ala	Ile	Gly			
					245					250					255				
	Arg	Leu	Gln	Leu	Arg	Thr	Leu	Lys	Gln	Gly	Asp	Lys	Glu	Ile	Gly	Pro			
				260					265					270					
5	Asp	Gly	Asp	Ser	Cys	Ala	Val	Cys	Ile	Glu	Leu	Tyr	Lys	Pro	Asn	Asp			
			275					280					285						
	Leu	Val	Arg	Ile	Leu	Thr	Cys	Asn	His	Ile	Phe	His	Lys	Thr	Cys	Val			
		290					295					300							
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#### PCT/JP99/03929

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PCT/JP99/03929

WO 00/05367

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#### PCT/JP99/03929

# 153/177

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# 155/177

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#### PCT/JP99/03929

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# PCT/JP99/03929

# 165/177

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	Leu Asp Asp Pro Thr Pro Asp Tyr Met Asn Leu Leu Gly Met Ile Phe	
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# 166/177

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PCT/JP99/03929

WO 00/05367

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#### PCT/JP99/03929

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#### PCT/JP99/03929

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# PCT/JP99/03929

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# PCT/JP99/03929

	Phe	e Ile	e Ile	∍ Th:	r Ala	a Ala	Thi	Val	l Gly	ту:	r Phe	∍ Ile	Phe	э Ту:	r Sei	r Ala	
					220	)				225	5				230	)	
	cga	agg	g cta	a egg	g aat	gca	aga	gct	caa	ago	agg	g aac	cas	g ago	J caa	a tta	951
	Arc	Arc	Leu	Arg	y Asr	Ala	Arg	, Ala	Gln	Ser	Arc	, Lys	Glr	ı Arç	g Glr	Leu	
5				235	5				240					245	i		
	aaç	gca	gat	gct	aaa	aaa	gct	att	gga	agg	g ctt	caa	cta	e cgc	aca	ctg	999
	Lys	Ala	Asp	Ala	Lys	Lys	Ala	Ile	Gly	Arg	Leu	Gln	Leu	Arg	Thr	Leu	
			250	)				255					260	)			
	aaa	caa	gga	gac	aag	gaa	att	ggc	cct	gat	gga	gat	agt	tgt	gct	gtg	1047
10	Lys	Gln	Gly	Asp	Lys	Glu	Ile	Gly	Pro	Asp	Gly	Asp	Ser	Cys	Ala	Val	
		265					270			•		275					
	tgc	att	gaa	ttg	tat	aaa	cca	aat	gat	ttg	gta	cgc	atc	tta	acg	tgc	1095
	Cys	Ile	Glu	Leu	Tyr	Lys	Pro	Asn	Asp	Leu	Val	Arg	Ile	Leu	Thr	Cys	
	280					285					290					295	
15	aac	cat	att	ttc	cat	aag	aca	tgt	gtt	gac	cca	tgg	ctg	tta	gaa	cac	1143
	Asn	His	Ile	Phe	His	Lys	Thr	Cys	Val	Asp	Pro	Trp	Leu	Leu	Glu	His	
					300					305					310		
		act												_			1191
00	Arg	Thr	Cys	Pro	Met	Cys	Lys	Cys	Asp	Ile	Leu	Lys	Ala	Leu	Gly	Ile	
20				315					320					325			
		gtg													-		1239
	Glu	Val	Asp	Val	Glu	Asp	Gly	Ser	Val	Ser	Leu	Gln	Val	Pro	Val	Ser	
			330					335					340				
0.5		gaa													-	_	1287
25	Asn	Glu	Ile	Ser	Asn	Ser	Ala	Ser	Ser	His	Glu	Glu	Asp	Asn	Arg	Ser	
		345					350					355					
		acc															1335
		Thr	Ala	Ser	Ser	Gly	Tyr	Ala	Ser	Val	Gln	Gly	Thr	Asp	Glu	Pro 🔔	
00	360					365				•	370					375	
30		ctg															1383
	Pro	Leu	Glu	Glu	His	Val	Gln	Ser	Thr .	Asn	Glu	Ser	Leu	Gln	Leu	Val	
				-	380					385					390		
		cat														_	1431
0.5	Asn	His	Glu	Ala	Asn	Ser '	Val .	Ala	Val .	Asp	Val	Ile :	Pro	His	Val .	Asp	
35				395					400					405			

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	aac cca acc ttt gaa gaa gac gaa act cct aat caa gag act gct gtt	1479
	Asn Pro Thr Phe Glu Glu Asp Glu Thr Pro Asn Gln Glu Thr Ala Val	
	.410 415 420	
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	425	
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	agagetattt aaaaatgeae tttatttgta etetgtgtgg ettttgtttt agaattttgt	2610
25	tcaaattata gcagaattta ggcaaaaata aaacagacat gtatttttgt ttgctgaatg	2670
	gatgaaacca ttgcattott gtacactgat ttgaaatgct gtaaatatgt cccaatttgt	2730
	attgattctc tttaaatata aaatgtaaat aaaatattcc aat	2773